QUANTIFYING THE INTER-INDIVIDUAL VARIATION IN RESPONSE TO EXERCISE INTERVENTIONS

Philip James Williamson BSc, MSc

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Teesside University

Health and Social Care Institute,
School of Health and Social Care

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Declaration

I declare that this thesis is entirely my own work and represents the results of my own research carried out at Teesside University. I declare that no material within this thesis has been used in any other submission for an academic award.

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Abstract

Interest in the concept of 'precision' or 'personalized' medicine has grown over the last three decades. While much of the literature published appears to support the notion that clinically-relevant individual response differences exist in phenotypes such as maximal aerobic capacity and weight loss, much of this research is based upon the observed response, as opposed to the 'true' inter-individual variation.

In this doctoral research programme, I investigated 'true' inter-individual variation in response to exercise interventions. The difference between observed and 'true' individual differences is that measurement error and other sources of random variation are fully considered in order to quantify 'true' individual differences. These were investigated due to the recent focus on 'individual responses and precision and personalised approaches. This was achieved through a number of approaches, including a critical review of literature, a systematic review and meta-analysis, and both secondary analysis of randomised controlled trial (RCT) data and primary data collection through the novel use of a replicate crossover trial.

A critical review of the relevant literature on responses of maximal oxygen uptake to exercise training revealed that when the correct method for statistical analysis is utilised on data from published research claiming substantial inter-individual variability in response, it was actually observed that there was greater variability in the control sample versus the intervention sample. This finding implies that there is no substantial true individual training response variance, though the uncertainty in the estimate of true inter-individual variability in response is marked with the small sample sizes involved. The review also revealed that the vast majority of published research purporting to show individual variation in response does not utilise the most robust trial design (RCT) or statistical methods (comparison of the standard deviations of the changes in all groups).

A meta-analysis of supervised exercise RCT's revealed that evidence is limited for clinically relevant 'true' inter-individual variation in weight change in response to an exercise intervention, once the random variability in weight over time in the control

group is accounted for. This was the first systematic review and meta-analysis of individual response variance. The pooled mean weight loss (-1.4 kg) was much smaller than a conservative threshold for a clinically important change (2.5 kg), and inter-individual variation in weight change standard deviation (SD) was only 0.8 kg. A novel approach using a prediction interval revealed that in a future study in similar settings, the 95% plausible range for mean weight change vs. control would be -5.0 to 2.1 kg. The probability that the mean weight change in a future study would be clinically relevant was 26% (possibly clinically important). For the individual response variability, the prediction interval ranged from small negative to small positive, and the probability that the individual response variance was clinically relevant was 23% (unlikely).

A secondary analysis of data from dietary and lifestyle advice interventions (PREMIER trial) revealed substantial inter-individual variations in the body weight and blood pressure responses. Paradoxically, this response variance was not even partially accounted for by including a sex-by-treatment interaction term in the model, despite substantial sex differences in mean treatment effect. When analyses were stratified by sex, much larger true individual response variance for weight loss and blood pressure changes were observed in men compared to women, explaining the paradox. The observed effect in women is relatively consistent, whilst in men it is much more variable, reinforcing the requirement for thorough exploration of data prior to undertaking full analyses.

In a novel replicate crossover trial designed to properly partition variance and quantify 'true' inter-individual variation in response to acute high intensity aerobic exercise, results suggest the presence of substantial 'true' inter-individual variation in response. There were large sex differences in mean response, with greater blood pressure and heart rate response variables in females in comparison to males. This was the first replicate crossover designed and analysed in this way, using a specific model to elucidate the acute response to exercise.

Evidence from these studies indicates that, when quantified appropriately, chronic exercise interventions appear to elicit limited 'true' inter-individual variation in response in peak oxygen uptake and weight loss. Conversely, there appear to

substantial inter-individual variations in blood pressure and heart rate responses to acute, high intensity aerobic bouts of exercise. Furthermore, with multicomponent interventions there appear to be substantial individual responses for blood pressure and weight loss in men, based on secondary analysis of existing trial data. It is clear that much of the research purporting to evidence individual variation in response is lacking a suitable control sample. To that end, in chronic exercise intervention trials, it is likely appropriate to focus upon the mean change, whilst for acute exercise interventions, further quantification of the magnitude of inter-individual variation in response may well be warranted.

Chapter 1: Introduction

1.1 Background

1.1.1 Inter-Individual Variation in Response to Exercise

Within the field of 'personalised', 'precision', or 'stratified' medicine, it is intuitive to think that different individuals respond to health interventions in different ways. A given health intervention may be beneficial, ineffective, or even harmful for different people (Rasool *et al*., 2015). The issue of inter-individual variation in response to an exercise intervention is, therefore, very important. Identifying those personal characteristics that may account for any clinically relevant variation in response may ultimately allow more efficient and ethical targeting of interventions to different people.

Interest in the concept of 'precision' or 'personalized' medicine has grown over the last three decades (Williamson *et al*., 2017). My own Scopus search has indicated that the number of published papers that include the words 'personalized medicine' or 'precision medicine' in the titles or abstract has risen from 4 in 1999 to 5772 in 2016 and 4747 in 2017. While much of the literature published on this topic over the last 30 years may appear to support the notion that clinically-relevant individual response differences exist, some researchers have based their conclusions on observed rather than 'true' individual differences in response. Essentially, the difference between observed and 'true' individual differences is that measurement error and other sources of random variation are fully considered in order to quantify 'true' individual differences.

The individual observed response that is often attributed to the intervention per se can include numerous sources of sometimes uncontrollable variability such as random (biological and measurement) variability, between-subject variability (if unadjusted for baseline), subject-by-treatment interaction and within-subject variability (Senn, 2016). However, it has previously been suggested that within-subject random variation can be so substantial that it actually explains all apparent individual variation in response (Atkinson & Batterham, 2015). Taking these factors

into account to derive the 'true' individual response difference is vital for robust inferences, conclusions and recommendations to be made in precision medicine (Atkinson & Batterham, 2015). Whilst this approach is a robust methodology for the quantification of the presence of inter-individual variation in response, the field has, so far, been slow to adopt this approach. This may be due to its novel nature, or its potential impact upon the findings presented within the literature.

1.1.2 The Concept of 'Precision' Medicine

Personalized, or precision, medicine has been forwarded as an alternative approach to current health models. This approach has the potential to reduce the prevalence of non-response.

This concept is often called *P4 medicine* (predictive, preventive, personalized, participatory). The overarching practical promise of 'P4' systems medicine is a revolutionary paradigm shift leading to a better overall utility of medicine, a better balance of benefits and harms. If successfully implemented, it could also allow for precise prescription of interventions to improve outcomes based upon technologies such as personal DNA–based testing, genotyping, and wearable micro-technologies, and allow decision making tailored to patients' individual requirements (Feero, 2007, Joyner *et al*., 2016). At the same time, it is envisioned as being based in primary care, and its promise of a revolution therefore depends on its ability to meet the challenges of current research, prior to implementation.

In 2015, President Obama launched the Precision Medicine Initiative (NIH, 2015), funded by an initial budget of $215 million. The initiative was described as having an 'innovative approach, that considers individual differences in people's genes, lifestyles, and environments', bringing us 'closer to curing diseases like cancer and diabetes'. He went on to describe how this approach would 'give all of us access to the personalized information we need to keep ourselves and our families heathier', in a 'new era, of medicine - one that delivers the right treatment at the right time'. Although precision medicine makes claims of changing the medical landscape, it currently exists mostly as a vision.

Some approaches in precision medicine have also been adopted for exercise research and prescription, and there have been attempts to quantify the inter-individual variation in response of human physiology, in order to identify moderators (such as sex and age) and mediators (changes in status from baseline) governing response variance. Unfortunately, in the exercise domain, this approach is based upon the as yet untested claim that clinically relevant 'true' inter-individual variation in response will always exist in an intervention. However, the current lack of robust research and the cost and highly specific nature of dedicated RCTs aimed at targeting and confirming intervention strategies mean that it is likely to be premature to state that precision medicine is the answer, especially given that without variation in phenotype response, further investigations to identify genetic interactions are pointless.

1.1.3 Health Implications of Exercise and Physical Activity

For many decades, there has been a public health burden incurred by poor diet, excess energy intake (EI), and sedentary lifestyles. These factors have been implicated in the higher risk of developing chronic diseases such as type 2 diabetes, cardiovascular disease, and an increased incidence of cancers (Alberti *et al*., 2007, Deram & Villares, 2009). The impact that these lifestyle-related diseases have on both society and individual quality of life remains substantial, as does the resulting financial burden (Douglas *et al*., 2016).

Physical activity, defined as any bodily movement produced by skeletal muscles that result in exergy expenditure (Casperson *et al*., 1985) and exercise – planned, structured and repetitive and with an objective (Casperson *et al*., 1985) have wide-ranging physiological benefits, such as improved maximal aerobic capacity, which can lead to primary and secondary prevention of a number of chronic diseases such as cardiovascular disease, diabetes, cancer, hypertension and obesity, and premature death (Warburton *et al*., 2006), in addition to decreased symptoms of depression (Craft & Perna, 2004). Whist the influence of physical activity and exercise is clearly wide-ranging, much of the focus of research has been on maximal aerobic capacity and cardiorespiratory fitness, as it is far more prognostic of future all-cause mortality (Kodama *et al*., 2009, Imboden *et al*., 2018).

Regular physical activity and exercise are the usually prescribed means of improving $\dot{V}O_2$max, with improvements recommended for both primary and secondary prevention of cardiovascular disease. The results of research indicate that a 1-MET (3.5 $mL.kg^{-1}.min^{-1}$) increase in cardiorespiratory fitness equates to a 12% reduction in cardiovascular disease and all-cause mortality risk (Myers *et al*., 2002). Similarly, an appropriate minimal clinically important difference (MCID) regarding a change in cardiorespiratory fitness of 1.1 $mL.kg^{-1}.min^{-1}$ can confer a 10% relative risk reduction in mortality (Laukkanen *et al*., 2016).

Healthcare has previously been delivered with a 'one-size-fits-all' approach (Bouchard & Rankinen, 2001, Pencina & Peterson, 2016), and research has reflected this approach in terms of the focus on the group mean effect of an intervention (Bouchard & Rankinen, 2001). Whilst this statistic informs the quantification of the general effect of an intervention, it may mask a range of responses for different people (Karavirta *et al*., 2011). Recent suggestions that traditional therapies may be ineffective for those with epigenetic causes of disease highlight the requirement for further study of the concept of inter-individual variation in response, with treatment for those individuals impacted potentially requiring personalized interventions (Rasool *et al*., 2015). The completion of the Human Genome Project has seen scientists prioritise the requirement to ensuring interventions are personalized, tailoring medical treatment away from the previously mentioned 'one-size-fits-all' towards interventions or treatments more likely to benefit the requirements of the specific participant.

1.1.4 Current Evidence

There have been reports that training studies consistently report a high variability in the effects of regular exercise training (Hecksteden *et al*., 2018), with reports of inter-individual variation of many physical characteristics, or phenotype, in response to various forms of exercise, such as aerobic training (Bouchard *et al*., 1999, Bouchard *et al*., 2000, Bouchard & Rankinen, 2001), resistance training (Hubal *et al*., 2005) and combined/concurrent training (Hautala et al., 2006); reports that exercise often results in less than expected weight loss for some individuals, or ranges of $\dot{V}O_2$max response of no change to 40% improvement (Lortie *et al*., 1984,

Bouchard & Rankinen, 2001). Additionally, researchers present plots and analyses that suggest large variation in physiological response, even when the magnitude of response variance is the same for all (Atkinson & Batterham, 2015).

However, there have been concerns raised in regard to the methodological approach of much of the previous body of research (Hopkins, 2015, Atkinson & Batterham, 2015, Williamson *et al*., 2017). The identification of factors that may explain inter-individual response variance should come only after true, substantial inter-individual differences in response have been demonstrated and quantified properly (Atkinson & Batterham, 2015, Williamson *et al*., 2017). This quantification requires an appropriate control/ comparator group, preferably within a randomised trial design, and comparison of the standard deviation of the change in outcome (SD_{change}) for each relevant group. Much of the published literature claims substantial treatment response heterogeneity based on analyses of changes in outcome in a single intervention group, with no inclusion of a comparator sample in the research design. Even worse is the ignoring the control data when available, when it is the presence of such that would provide the required counterfactual (Williamson *et al*., 2017).

Claims that precision medicine is the answer to this current hot topic are likely premature, based upon the lack of evidence obtained utilising the RCT approach, as this methodology allows for comparison of the intervention arm with a relevant control group, over the same time course (Hopkins, 2015, Atkinson & Batterham, 2015). Variability in the responses to exercise exists if the variability in observed response exceeds the variability in observed responses in a control sample (Atkinson & Batterham, 2015) However, if, following an RCT, substantial variation in phenotype response does not exist, it is pointless looking for genetic interactions (Senn, 2004). Additionally, it could be questioned whether further investigation in this case would be ethically sound.

1.2 Rationale for the Thesis Topic and Research Questions

Given the claims of inter-individual variation in response in a number of studies, and the recent criticisms of the analysis of these (Hopkins, 2015, Atkinson & Batterham,

2015), it is clear that proper quantification of the 'true' inter-individual variation in response to exercise interventions is required.

Outcomes in maximal aerobic capacity, weight loss and blood pressure are investigated due to their prognostic value for health. Additionally, the bulk of published research in this area focus upon maximal aerobic capacity and weight loss. The primary focus of this research project is to interrogate these claims, and to fully elucidate the presence of 'true' inter-individual variation in response to exercise interventions, based upon the methods of analysis recently suggested (Hopkins, 2015, Atkinson & Batterham, 2015).

Several common limitations can be identified within many of the studies investigating the inter-individual variation in response to a chronic exercise intervention.

Almost exclusively in these studies, a control group is either absent or discarded in the data analysis (Williamson *et al*., 2017, Williamson *et al*., 2018). As is highlighted in this thesis, the inclusion of data from a comparator group to compare the inter-individual response to the given intervention is of principal importance in a chronic response trial. In this thesis I aim to rectify this gap in the literature. Additionally, in the investigation of acute effects of exercise, no study with a replicate crossover design has been undertaken in order to elucidate the inter-individual variation in blood pressure response immediately post-exercise, nor has any research been undertaken purporting to investigate the inter-individual variation in acute blood pressure response to exercise. This thesis includes an original study and a secondary data analysis that applies an appropriate method to achieve this aim and is accompanied by discussion and practical implications of the findings of this novel approach.

1.3 Aims and Objectives of this PhD and Experimental Approach

The main aim of this PhD is to investigate the appropriate quantification of inter-individual differences in the response to exercise interventions, as well as the exploration of putative moderators and mediators of both the mean intervention

effect and the individual response, where appropriate. Approaches to identifying 'positive responders', 'non-responders' and 'adverse responders' to interventions will also be investigated where appropriate.

Specific objectives:

1. To critically review the literature on inter-individual variation in maximal aerobic capacity response to exercise.
2. To undertake a systematic review and meta-analysis of weight change literature, with a focus upon quantifying the inter-individual variation in weight loss.
3. To conduct detailed and rigorous secondary data analysis of previously published data set from the PREMIER research project, using state-of-the-art analysis techniques to identify and quantify 'true' inter-individual variation in weight loss and blood pressure response to the interventions.
4. Design and undertake a pilot/'proof-of-concept' investigation to investigate the acute inter-individual variation of blood pressure and heart rate variables in response to high-intensity aerobic interval training, using a replicate crossover design, in order to test and validate a statistical model to fully partition the various sources of variance and to isolate 'true' inter-individual variation in response to high-intensity aerobic interval training, an approach that has not been previously achieved. Successful partitioning of variance in the repliucate crossover will provide a model that can be used as a basis for future research.

1.4 Structure of the Thesis

This thesis consists of eight chapters. This chapter (Chapter 1) constitutes the introduction, and discusses the background, rationale, and aims and objectives of the study. Chapter 2 presents a focused literature review, providing a historical overview, key concepts, a review of previous research, and background to the utilisation of analysis of the inter-individual variation in response to exercise. The reader will find a detailed review discussing precision medicine, aerobic capacity and the investigations carried out in this area, obesity and its genetic base, the effects of exercise on blood pressure, the underpinning physiology, and outlining the

previously published research purporting to investigate the inter-individual variability in response to exercise interventions upon these variables. Chapters 3 – 7 consist of investigations of the relevant outcome measures that were studied as part of this doctoral programme. This work includes a critical review of the inter-individual variation of maximal oxygen uptake in response to exercise training (Chapter 3), a systematic review and meta-analysis into the exercise and weight loss literature (Chapter 4), a secondary data analysis of blood pressure and weight loss variation (Chapter 5), and findings from a proof-of-concept pilot replicate crossover design study investigating the acute inter-individual variation in blood pressure response to high intensity aerobic exercise(Chapter 6). Chapter 7 forms the overall discussion, bringing together the findings of the thesis, as well as strengths of the findings presented. In this chapter, I also elaborate and critically synthesize the findings of the thesis and discuss limitations and provide directions for future research.

Recommendations for both practice and research are provided, in addition to justification of how this research provided an original contribution to knowledge. Finally, appendices are attached, including published papers and abstracts from conference proceedings, with complete details provided of items discussed within the thesis.

1.5 Potential Impact

Given the stated rationale for this thesis, it is important at this time for the claims of inter-individual differences in response to an exercise intervention, with a particular focus on maximal oxygen uptake, weight loss, and blood pressure response, to be scrutinised in the context of recent criticisms. Identification of the presence of clinically important inter-individual variation in response would allow for the development of appropriate research design for investigation of potential moderators and mediators. Alternatively, confirmation of the absence of such would allow for research funding to be diverted to more appropriate sources.

The findings from the work presented in this thesis have the potential to increase the understanding of the methods and statistical approaches that may be employed to

correctly quantify the ‘true’ inter-individual variation in response to an exercise intervention in both acute and chronic training studies. This, in turn, will help to clarify the classification of ‘non-responders’, and to guard against spurious assumptions or incorrect methodological approaches. Furthermore, given the focus upon precision medicine, policy and both applied and academic practice may be changed based upon the findings of this programme of work. If clinically-relevant individual response differences are not supported, then the commitment to funding further research on aspects of this topic may be questionable.

Chapter 2: Literature Review

2.1 General Overview

It is generally assumed that individuals respond in a consistent manner to treatment (Senn, 2004). However, all individuals acquire a variety of characteristics (Hopkins, 2015). The potential that this could lead to gene-polymorphisms accounting for inter-individual differences in response has been discussed previously (Mori *et al*., 2009). Nevertheless, it is important not to overreact to apparent differences (Senn, 2016), as these may be due to a number of factors, such as random within-subjects' variation, from sources such as technical error and random within subjects' biological variation. In this literature review I begin by addressing 'precision medicine' before discussing the concept of individual variation of maximal aerobic capacity, body mass, and blood pressure variables in response to chronic and acute exercise.

2.2 Precision Medicine

Until recently, healthcare interventions such as medication and exercise have been undertaken with a 'one-size-fits-all' approach (Bouchard & Rankinen, 2001, Pencina & Peterson, 2016). Most researchers focus upon 'main effects' and mean group changes (Bouchard & Rankinen, 2001), without analysis of individual participants. The focus on individual response may be of benefit (Pencina & Peterson, 2016), particularly if clear differences in response between an intervention sample and a comparator sample are evident. This approach is useful but does not allow us to distinguish between individuals (Senn, 2004), and may hide a wide range of responses (Karavirta *et al*., 2011), as effects documented at group level may not apply equally to every individual within the group. Large amounts of empirical evidence may have been ignored due to this focus upon mean changes, and it has been proposed that standard statistical analysis and methodological training has left researchers unaware of the significance of response heterogeneity (Bryk & Raudenbush, 1988). Over the last three decades, interest has grown exponentially, with Scopus searches revealing that papers published including the words

‘personalized medicine’ or ‘precision medicine’ have risen from 4 in 1999 to 5772 in 2016.

It has been suggested that traditional therapies may be ineffective for those with epigenetic causes of disease, and treatment for these individuals may require personalized or genomic medicine (Rasool *et al*., 2015). Over the past decade, following the completion of the Human Genome Project (www.genome.gov), an international, collaborative research program (Collins & McKusick, 2001) which entailed the mapping and understanding of all human genes to determine the sequence of the human genome and identify its components parts, there has been a move by scientists and officials towards ensuring medicine is more personalized (Hamburg & Collins, 2010, Blaus *et al*., 2015, Buford *et al*., 2013, Collins & Varmus, 2015). This practice involves tailoring medical treatment away from ‘one-size-fits-all’ towards treatment strategies most likely to benefit the individual (Blaus *et al*., 2015), using the technological and scientific advancements in the fields of genetics, medicine, science and health care (Marcon *et al*., 2018).

In his State of the Union address in 2015, President Obama launched the Precision Medicine Initiative (NIH, 2015, Precision Medicine Initiative Working Group, 2015) , an “innovative approach, that takes into account individual differences in people’s genes, lifestyles and environments” to “bring us closer to curing diseases like cancer and diabetes, and to give all of us access to the personalized information we need to keep ourselves and our families heathier”, in a “new era, of medicine-one that delivers the right treatment at the right time”. An initial budget of $215 million was invested to support these efforts. Similarly, then-Prime Minister of the United Kingdom, David Cameron, had previously announced the coalition government’s effort to sequence the 100,000 human genomes (100,000 Genome Project, genomicsengland.co.uk) by the end of 2017, aimed at making the National Health Service the world’s first healthcare system to launch a genomics medicine service. This initiative was then to be built upon and a focus upon permanently embedding genomics in care was suggested (National Health England, 2015). However, this approach has numerous obstacles. Scientific challenges, such as the accurate determination of specific genes with clinical importance, policy challenges such as

regulating genetic testing and ensuring rigorous validity and reliability of such tests are paramount (Hamburg & Collins, 2010).

2.2.1 Definition of 'Precision Medicine'

The terms 'precision medicine' and 'personalized medicine' have been used interchangeably in the US and the UK (McCartney, 2017). Whilst as yet undefined, the National Institutes of Health currently states that it is 'an emerging approach for disease treatment and prevention that considers individual variability in environment, lifestyle and genes' (NIH, 2015), whilst a National Research Council report suggests it 'refers to the tailoring of medical treatment to the individual characteristics of each patient' (NRC, 2011). It has also been described as 'prevention and treatment strategies that take individual variability into account' (Collins & Varmus, 2015). Precision medicine may allow the combination of components from various emerging sub-disciplines such as real-time monitoring, diagnostic tests, and data analytics to improve desired outcomes (Montalvo *et al*., 2017).

2.2.2 Use of Precision Medicine

Precision medicine has been suggested as an alternative solution to current health models, under the premise of improved prediction, prevention, diagnosis and treatment of disease, based upon wearable technology (Feero, 2017), genotyping, and DNA variants (Joyner, 2016). It is currently claimed that personalized medicine has improved diagnostics, drug development, and risk assessment and modification (Chan & Ginsburg, 2011); however, the number of variants and the relative impact of each of these on disease development is yet to be clearly elucidated, meaning that, at best, it may be prudent to target groups (stratify) rather than individuals. It has also been assumed that this approach will reduce the cost of healthcare; however, it is still an expensive concept (Kittles, 2012) and the cost of screening for specific genotypes and specialized healthcare cover may, conversely, increase healthcare costs.

Successful precision medicine, therefore, would allow for the optimization and customization of health care, using emergent technologies to make decisions tailored

to the patients' individual requirements (Arnason, 2012, Mauri *et al*., 2014, Jameson & Longo, 2015, Collins & Varmus, 2015), enabling patients and general public to participate in both treatment decisions and preventative behaviour (Collins & Varmus, 2015). If successful identification of a precise biomarker is achieved, those that may benefit from a specific intervention may be recognised. Tailored pharmacokinetic (the time course of drug absorption, metabolism and excretion) or pharmacodynamic (the relationship between drug concentration and the relative effect) response-based therapies could then be applied (Blaus *et al*., 2015), if the drug response of an individual were accurately predicted (Spear *et al*., 2001). If this is, indeed, the case, predictive methods of directing individuals towards treatments with likely higher treatment efficacy could then also be derived, with small increases in resulting response having dramatic effects upon disease burden.

It has been suggested that precision or personalized medicine claims hint at radical transformation in medical care and public health (Joyner & Paneth, 2015). This change would occur through reducing system costs and improving health care efficiency (Keogh, 2012, Flores *et al*., 2013, Hood *et al*., 2015), treatment and disease prevention programmes developed by the creation of large biobanks, genome sequencing, and the use of biological information to link to medical records. Conversely, criticisms of precision medicine question the value of its use in many contexts (Joyner, 2016, Prasad, 2016). It has been highlighted that inappropriate shifts in emphasis from public health initiatives to individual focus (Arnason, 2012, Tedstone, 2016), and the lack of a definition of 'normality' (Manrai *et al*., 2018), may result in over diagnosis and unnecessary testing (Diamanndis & Li, 2016). A further drawback is that much of the gene data collected is focused upon individuals of European ancestry (Kittles, 2012), and it is unknown as the extent of regional differences in health risk profile.

2.2.3 Precision Medicine and Exercise?

Whilst precision medicine has primarily been concerned with the heterogeneity of response to medication (Buford *et al*., 2013), the use of exercise for precision treatment is a novel concept. As the focus on 'main effects' may miss important individual level information, a focus upon the quantification of inter-individual

variation in response has grown in recent years (Williamson *et al*., 2017). It has been postulated that precision medicine may be used to personalize training for elite performance (Montalvo *et al*., 2017), as several single nucleotide polymorphisms (SNP) associated with exercise induced muscle damage have been identified; with knowledge of this, a practitioner could potentially maximise training prescription and reduce injury risk (Baumert *et al*., 2016).

The interest in precision medicine has also stimulated attention in the exercise and public health domain, and the quantification of inter-individual variation in response of human physiology (Deighton *et al*., 2017, Hecksteden *et al*., 2018). The purpose of research around precision medicine is to identify genetic factors governing response variance; however, this is founded on fundamentally untested (as yet) assumptions that 'true' inter-individual variation in response exists. Currently, given the lack of information regarding the impact of genetics on many diseases or population health outcome variables, the cost and highly specific nature of dedicated RCTs aimed at targeting and confirming intervention strategies (Pletcher & McCulloch, 2017), and the incredibly complex nature of disease pathogenesis (Khoury & Galea, 2016), it is likely to be premature to state the case that precision medicine is the answer to this current hot topic. Furthermore, if the required variation in phenotype response does not exist, it is pointless looking for genetic interactions (Senn, 2004).

2.3 Previously Utilised Methodological Approaches

2.3.1 Use of Comparator Arm

The concept of inter-individual variability in response to exercise was first mooted during the 1980s (Prud'homme *et al*., 1984, Despres *et al*, 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Bouchard *et al*., 1986, Hamel *et al*., 1986, Simoneau *et al*., 1986), with claims of inter-individual response in cardiorespiratory fitness, lipolysis, glucose conversion, and fibre-type conversion. These variations were attributed to genotype dependency. However, despite an apparently growing body of evidence, in recent years the veracity of the approach to quantifying inter-individual variability in

response to exercise has been questioned (Hopkins, 2015, Hecksteden *et al*., 2015, Atkinson & Batterham, 2015, Williamson *et al*., 2017).

Based upon these early studies, it is now assumed that there are considerable inter-individual differences in response (Bouchard *et al*., 2015); however, this may or not be true for any particular study (Atkinson & Batterham, 2015, Williamson *et al*., 2017). Previous studies have assumed that the inter-individual variability in response for a given trait is solely a consequence of exercise interventions. Others maintain that the presence of inter-individual variation in response to an intervention must be properly quantified before the exploration of moderators and mediators of variation in response are investigated (Atkinson & Batterham, 2015). Indeed, the often-utilised, no-comparator sample approach ignores the random variability (biological and measurement error) over the time course of the intervention.

Much research has claimed the presence of inter-individual variation in response, by analysing data from an intervention sample only (Bouchard & Rankinen, 2001, Sisson *et al*., 2009, Pandey *et al*., 2015). This approach is wasteful and likely misleading (Atkinson & Batterham, 2015). It has been stated that comparison of intervention group variability with control group variability is necessary to adequately quantify inter-individual variability in response to exercise (Hopkins, 2015, Hecksteden *et al*., 2015, Atkinson & Batterham, 2015, Williamson *et al*., 2017). For chronic training interventions, it has recently been described how the most appropriate approach to quantifying the inter-individual variation in response is by conducting a randomized control trial (RCT), as this methodology allows for comparison of the intervention arm with a relevant control group, over the same time course (Hopkins, 2015, Atkinson & Batterham, 2015). Specifically, variability in the responses to exercise exists if the variability in observed response to exercise exceeds the variability in observed responses to a control sample (Atkinson & Batterham, 2015, Williamson *et al*., 2017). Without the comparator arm, it cannot be stated with any confidence that any individual in the intervention arm may be a responder, as what would have happened to that person had they been in the control sample – the counterfactual -is not known (Williamson *et al*., 2017).

It has been posited that focusing solely on the intervention arm to determine responders and non-responders turns a parallel group RCT into a ‘single arm’ study

(Norbury & Seymour, 2018). However, the parallel group RCT allows for interpretation of what would likely happen, on average, to participants in the intervention arm if, contrary to the fact, they were in the comparator sample (Atkinson & Batterham, 2015). Exclusively, previous trials have ignored this comparison and, therefore, have not accounted for the contribution of random variability over time for the given outcome under study. Thus, whether inter-individual variability attributed to exercise exists after accounting for random variability is unknown.

The analytical limitations of prior trials have been addressed by proposing a standard statistical approach that separates the random variability from the intervention variability by using standard deviations (SD) of the changes from both the control and intervention groups (Atkinson & Batterham, 2015). Therefore, to fully investigate the magnitude of inter-individual response and separate the variation due to random error (present in both control and intervention) from the variation due intervention alone, the appropriate method to quantify 'true' individual response variability in a parallel group study involves the application of the following equation; $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$ (Atkinson & Batterham, 2015, Hopkins, 2015). In this equation, SD_{IR} is the true inter-individual response variability, I is the intervention sample and C is the comparator (control) sample. The SD_{IR} should be interpreted as the amount by which the mean effect of the intervention (intervention minus control) differs between individuals (Hopkins, 2015). The SD describes the 'typical' inter-individual variation in response between each participant (Atkinson & Batterham, 2015), and when SD_{IR} is calculated, it represents the typical 'true' inter-individual variability, adjusted for random biological variation and measurement error (Hopkins, 2015). This approach controls for regression to the mean (Atkinson & Taylor, 2011, Atkinson *et al*., 2015). A larger SD of changes in outcome in the intervention group would indicate a greater magnitude of inter-individual variation vs the control sample (Hopkins, 2015), and may therefore indicate further investigation of the moderators (effect modifiers) and mediators of this variation is warranted.

The standard analysis of a parallel-arm RCT is an ANCOVA analysis adjusting for chance imbalances in the outcome at baseline. In this analysis, the SD_{IR} is derived

using a linear mixed model, as described in Atkinson & Batterham, 2015. In essence, in this model the SD of the changes in intervention and control arms are adjusted for chance imbalances at baseline.

2.3.2 Identifying 'Responders' and 'Non-Responders'

The concept of inter-individual variability creates the issue of how to characterize 'responsiveness' in individuals. Dichotomously characterising in such a way is inherently irrelevant to prognostic risk, as this is most likely continuous, rather than binary, in nature (Sisson *et al*., 2009). Furthermore, insufficient information on the partitioning of variance is elicited (Norbury & Seymour, 2018), meaning consideration of data presented in this manner may be inappropriate.

Individuals have been described as 'responders' or 'non-responders' based on the changes seen in a single phenotype (Mann *et al.*, 2014). This approach may help identify individuals or 'sub-groups' that benefit from an intervention (despite no apparent mean improvement). However, there is a lack of clarity regarding the criteria used to categorise individuals. Labelling individuals as 'non-responders' based on the change in a single variable can be also misleading, given the various physiological adaptations often observed in response to acute and chronic exercise. To that end, the magnitude of response across a range of phenotypes should be investigated (Mann *et al.*, 2014).

An often-utilised approach to determining non-response to exercise is the setting of a statistical quantification of test-retest variability, such as 2 x typical error (TE) (Alvarez *et al*., 2017, Bonafiglia *et al*., 2016, Gurd *et al*., 2016) or technical error of measurement (TEM) (Bouchard *et al*., 2012) as a threshold for response. The proportion of individuals whose response is identified to be below this arbitrary threshold are then often defined as 'non-responders'. This sample is then compared between various intervention groups, instead of a relevant comparator sample taken over the same duration as the intervention, in the belief that a comparison of inter-individual responders is being undertaken. Using this test-retest variability is problematic, as that used is often based upon 3-day variability (Gagnon *et al*., 1996), as opposed to the same duration as the training intervention. Random within-subjects' variation would be expected to be substantially greater over an intervention

lasting, say, 12-24 weeks than over 3 days. Even when this 3-day test-retest technical error of measurement value has been used to set a threshold, random within-subjects variability is disregarded when portions of 'non-responders' are calculated. There will naturally be individuals showing changes of lesser magnitude than the test-rest variability but are not considered when calculating portions of 'non-responders'. The TE will also likely not coincide with a threshold for clinical or practical importance. Ideally, magnitude of response should be compared to a minimal clinically important difference (MCID), anchored to a clinically relevant risk reduction. This MCID is often derived from the epidemiological literature, however, if it is not, an acceptable default approach is to use 0.2SD of the baseline pooled SD is an acceptable approach for identifying the smallest worthwhile change (SWC) (Hopkins, 2004). Similar concerns can be raised about other studies (Bonafiglia *et al*., 2016, Alvarez *et al*., 2017) using this approach, or the use of observed changes greater than the coefficient of variation (CV) for a particular phenotype (Astorino & Schubert, 2014) to determine 'responders' and 'non-responders'.

It should also be considered that whilst the main outcome of any intervention may produce some who do not 'respond' as much as others, other physiological variables may well show improvement (Buford *et al*., 2013). Additionally, response may well be dose-dependent. Greater intensity (Ross *et al*., 2015) and volume (Pandey *et al*., 2015) have both reduced incidence of 'non-response', and these individuals presenting lower sensitivity or adaptation to an intervention may simply require a greater stimulus. This may be a further confounding variable to be addressed.

2.3.3 Eliminating 'Non-Responders' or Shifts in the Mean?

The effects of exercise training dose in cardiorespiratory fitness responsiveness in healthy young males after selected repeated 6-week interventions was recently explored (Montero & Lundby, 2017). These authors reported a decrease in the incidence of 'non-response' to endurance training with higher exercise dose, which they claimed was completely absent in those undertaking the highest doses of exercise (240 and 300 minutes per week) after the first 6 weeks. Based upon these findings, the authors suggested that the lower levels of the current exercise guidelines may not provide a sufficient stimulus to evoke positive adaptations in all

individuals (69%, 40% and 29% respectively classified as ‘non-responders’ for groups 1, 2 and 3, compared to 0% and 0% for groups 4 and 5 when considering maximal power output). It was also stated that the incidence of ‘non-response’ to endurance training was completely eliminated following a second 6-week training period, therefore concluding that improvements may be elicited in ‘non-responders’ by using higher training stimuli.

However, similarly to many previously reported studies, no control group was included in the study, instead using data from a short-term test-retest reliability study; the inclusion of a suitable comparator sample is crucial to separate inter-individual variability in CRF response to endurance training from the random error component and, thus, control the sources of variation that may affect the study results. Indeed, in this case, variation will likely be conflated over time, highlighting why comparator data collected over the same time period as the intervention in crucial. Additionally, the self-selecting intervention group removes the highly important randomization process from the trial design.

Whilst claims for elimination of ‘non-response’ are made, the authors overlook the fact that the whole distribution of responses changes when the mean response itself changes, hence the decreasing proportion of non-responders as the mean response increases. The authors appear to confuse shifts in the whole distribution as exercise volume increases with true individual differences in the response to a given intervention. Essentially, as the distribution shifts to the right, everyone becomes a responder.

Furthermore, the authors appear to have run a ‘replicated’ intervention study to facilitate eradication of ‘non-response’ in those showing less than 1xTE improvement in peak power output (without the proper design that would have allowed them to quantify the subject-by-training interaction (Hecksteden *et al*., 2015)). Five intervention groups were included, but, as stated, no control group, thereby assuming that the threshold concept for individual training response would have been a valid approach to draw solid conclusions about inter-individual variation in cardiorespiratory fitness response. This approach to distinguish between ‘responders’ and ‘non-responders’ is clearly flawed, as pre-post design studies

require analysis of the SD of the respective change scores in comparison with that of a suitable comparator sample (Hopkins, 2015, Atkinson & Batterham, 2015), whilst replicate crossover studies to elucidate inter-individual variation in response require specific statistical modelling, such as that proposed by Stephen Senn (2016). Additionally, the study was not actually a replicated crossover designed for the identification of inter-individual differences, as the different conditions used were at different exercise intensities rather than the same intensities replicated. It is also clear that a crossover-based trial cannot be used for chronic training studies, given participants are starting from a different baseline, due to chronic adaptations (Williamson *et al*., 2017). It can, however, be employed in the investigation of acute responses to exercise.

2.3.4 Consideration of Within-Subject Variability

Although the equation presented by Hopkins (2015) and Atkinson & Batterham (2015) accounts for random variability, the within-subject variability in treatment response remains. It is important to note that the implicit assumption for exercise interventions examining individual response is that the training effects among individuals are highly reproducible. It is possible that the observed individual variability is, in fact, due to variable responsiveness to treatment within each individual. This begs the question - would an individual respond similarly if they were to repeat the same intervention? This question remains unanswered.

To assess within-subject variability, participants would have to repeat the intervention after an appropriate washout period to determine whether individuals would respond in a similar manner. Thus, the proper separation of subject-by-treatment interaction from within-subject variability can only be achieved through repeat administrations of the intervention to the same individuals. Furthermore, a large scale multi-period (replicate) crossover intervention design is, in fact, the only study design that can adequately identify all forms of variability discussed above with the addition of treatment variability as well (variability of the differences between each treatment phase). However, this type of intervention design is not practical or may not even be feasible to carry out due to high participant burden, cost, and uncertainty regarding washout periods for training adaptions that may or may not become permanent. As it stands, it remains difficult to delineate potential

within- subject variability from subject-by-treatment variability with current RCT designs due to the inability of an RCT to fully partition variance.

As an alternative solution, Hecksteden *et al*. (2015) suggest that repeat testing of outcome measures throughout the duration of the intervention can help account for within-subject variability by comparing segmental slopes of change scores for shorter durations across the treatment period. However, this approach is also limited. First, the close temporal proximity of the measures may lead to high amounts of autocorrelation (measure of randomness) and a violation of the assumption of random errors. Additionally, training adaptions may not necessarily be linear over the course of the intervention and repeat measures may be expensive and impractical for some interventions. When this repeated assessment approach was recently utilised (Hecksteden *et al*., 2018), the analysis and inferences made appear flawed, as exercise response at 12 months is compared with control response at six months; given that the rise in SD from months 6-12 in the exercise is clear, it would be prudent to suggest that similar increases would therefore also be expected in a non-exercise control sample during the same period, therefore resulting in an inflated SD at 12 months. This highlights the folly of attempting to make inferences from different time points in exercise vs control. The authors also state that that non-responders are labelled such if they show a response in "an unexpected direction", when realistically, if non-responders were present, they would be identified by either not improving as much as a threshold for clinical relevance, or, when using Hopkins' approach (2015), when a substantially lower probability of being an individual responder may be assigned. For now, doubts remain over whether this approach provides a plausible alternative to conducting a repeated cross-over design intervention or conducting a separate reliability intervention trial. In an applied setting, practitioners may look to utilise either approach, as long as they are aware and state the strengths and limitations of the methodology they select, and make appropriate inferences based upon these strengths and limitations.

2.3.5 The 50% Heritability Claim

There is a growing interest in individual response differences and exploring potential predictors of these individual responses. A recent opinion piece (Pickering & Kiely, 2017) discussed talent identification, and the ability to adapt to exercise. Key within

their discussion was a focus on the inter-individual variation in capacity to improve physical characteristics as a key to future talent identification programmes. They went on to discuss genetic profiling which may, in their view, allow identification of those with the greatest potential for improvement, based upon the assertion that exercise adaptation is partially genetically driven.

The argument for selecting athletes based upon future athletic potential, rather than current high-performance, has its merits, given the non-linear nature of maturation. However, use of genetic profiling and the companies purporting to provide such information as to predict future athletic development is virtually meaningless. It is also largely without scientific foundation, and the use of direct-to-consumer (DTC) genetic testing to define or measure genetic risk for common diseases or developing personalized diet and lifestyle recommendations (Janssens *et al*., 2008), alter training, or for talent identification has previously been warned against due to lack of evidence on their efficacy and possible commercial misrepresentation (Webborn *et al*., 2015). Results from a recent study indicated that 40% of variants used in a diagnostic approach in a variety of genes reported in DTC raw data were false positives, whilst some genes classified as 'increased risk' were, in fact, benign or noted to be common variants (Tandy-Connor *et al*., 2018). Whilst having access to raw genotyping data may be informative and empowering for individuals, this information can be misinterpreted, misleading and wholly inaccurate. Those providing DTC testing also often ignore both the weak predictive power of the tested genes and the complexity of relevant genetics, with minimal information provided on how one might use the test results to makes changes to lifestyle or why the testing is effective. It is clear that this approach adds little in terms of value to individual or population health at this time.

The claims that "approximately 50% of baseline maximal oxygen uptake ($\dot{V}O_2max$) is heritable" (Pickering & Kiely, 2017) appear to be re-interpreted to suit the argument presented by these authors. The study this information is taken from actually states that "the heritability of $\dot{V}O_2max$ among sedentary adults could be as high as 50% although this value is undoubtedly inflated by non-genetic familial factor" (Bouchard *et al*., 2000). Indeed, this study was an ACE gene study in which it was concluded that there was no association at all between genes and response,

concluding that although there is no direct evidence to support the notion that ACE genes were involved in human trainability, it could be hypothesized that they contribute to inter-individual variation in training response.

The aforementioned claims are also similar to those made in a recent meta-analysis, where it was stated that 'it has been estimated that $\dot{V}O_2$max trainability has a significant heritable component of around 50%' (Williams *et al*., 2017), and which worryingly have now been progressed to 'at least 50% of adaptation responses to endurance training are heritable (Vellers *et al*., 2018). Conversely, whilst ranges of 44-68% heritability have been described in a recent meta-analysis (Miyamoto-Mikami *et al*., 2018), due to the lack of explanation elucidated through analysis of the studies included in their meta-analysis, these authors suggest further studies are required in order to clarify this heterogeneity.

I have questioned the findings of much of the published literature from the HERITAGE Family Study, from which these '50%' claims originate, in regard to change in $\dot{V}O_2$max in Chapter 3 of this thesis and in a published critical review (Williamson *et al*., 2017). Many of the highlighted limitations centre upon the lack of a control group with which to make comparison of the SD_{change}, and therefore elucidation of any inter-individual variation in response to exercise. As is discussed repeatedly in this thesis, in order to calculate the true inter-individual variation in response to an intervention, in a parallel group study, true inter-individual difference in response is only present if the response variance in the intervention group is substantially larger than that in the control. The square root of the difference in response variance (intervention minus control) gives the SD of the individual response, or the variability in response which surpasses expected random within-subjects variability (Atkinson & Batterham, 2015). If there are no substantial differences between the two, the observations of inter-individual variation in response can actually be described as baseline-to-follow-up within-subjects variability (Atkinson & Batterham, 2015), which may be influenced by growth, maturation and physical development.

Pickering & Kiely suggest that the magnitude of training response differs greatly between individuals, and this information can assist in the identification of the

'talent' of adaptation. Again, this statement is based upon the findings presented in the HERITAGE Family Study (Skinner *et al*., 2001) and I discuss how response should be defined in regard to a minimal clinically worthwhile difference (MCID) in Chapters 3 and 4. In brief, for a given individual, the observed change in phenotype following an intervention can be combined with knowledge of the natural random variation in that phenotype over the same time period (from a control group or similar reliability study) to derive the probability that this individual's true response is greater than the MCID (Atkinson & Batterham, 2015).

Pickering & Kiely also suggest that the X allele of the α-actinin-3 (ACTN3) gene may be responsible for those with larger adaptations in $\dot{V}O_2$max, whilst Williams *et al*., (2017) state that 97 genes are identified as possible predictors of $\dot{V}O_2$max trainability. However, it is concerning that data mining in this manner, presumption of this figure of (now 'at least') 50% heritability in regard to $\dot{V}O_2$max training response, and subsequent research into the genetic mediators of this response, may be unwarranted and potentially misleading. It must also be remembered, that while genetic factors may influence training response, due to their individual small effect sizes, any one genetic variant will likely only contribute a tiny amount to any variability. Rather, further research should be carried out to test the '50%' hypothesis, in the presence of a suitable comparator sample, observed over the same duration of any intervention group.

Such claims of genetic basis for individual variation in response, or trainability of phenotypes such as maximal oxygen uptake should be made with caution and based solely upon research that has reported these findings utilizing suitable research design. Assumptions of '50% of heritability in trainability' should also be made with the utmost of caution, and the use of DTC genetic testing for talent identification should not be recommended at this time.

2.3.6 Partitioning Variance

If we wish to use an individual's results, such as that seen in an *n*-of-1 trial, in order to prescribe an appropriate exercise intervention, response measurement in isolation is not sufficient. We must first understand the components of variation. The design

of a multi-period crossover with a mixed (fixed and random effects) analysis model would be more suitable for the efficient estimation of treatment effect (Senn, 1993). This would allow for the partitioning of various components (between treatments, between patients, patient-by-treatment, within patients) of variance (Senn, 2016). This approach is also useful for quantifying the inter-individual variation in acute response to exposure to exercise, and is an approach utilized in Chapter 6 of this thesis.

2.4 Genetics, Heritability and Maximal Oxygen Uptake

It has been proposed that genetic variations may determine change in aerobic fitness (Zadro *et al*., 2017). ACE polymorphisms have been suggested to be linked to elite aerobic (rowing) performance (Gayagay *et al*., 1998), whilst SNPs rs2267668 in peroxisome proliferator-activated receptor-δ (*PPARD*) and Gly482Ser in peroxisome proliferator-activated receptor-γ coactivator 1α (*PPARGC1A*) have been claimed to have independent impacts upon the effectiveness of exercise to improve physical fitness (Stefan *et al*., 2007), and *PPARGC1A* and Gly482Ser have been suggested to predict exceptional endurance capacity (Lucia *et al*., 2005).

Recent suggestions include the need for research into the contribution the mitochondrial genome may have on genetic regulation of the variation in exercise adaptation (Vellers *et al*., 2018). Specific genes responsible are yet to be identified, but Bouchard (2012) suggested that a genomic predictor score based on alleles carried at 21 single nucleotide polymorphisms may assist in identifying high and low training responders. However, further confounding these claims, to date, only a few genome-wide association studies have been published using $\dot{V}O_2$max response as a trait, and all of these have been based upon the data collected from the HERITAGE participants (Timmons *et al*., 2010, Bouchard *et al*., 2011, Ghosh *et al*., 2013).

2.4.1 Use of Siblings to Understand Heritability

Studies of siblings have been used to make inferences about the importance of genetic influence in heritability (Simoneau *et al*., 1986), where the reported *F*-ratios suggested 5-10 times more variance between twin pairs than within pairs. Similarly, genetic determination has been claimed for several different aerobic performance

measures from the results of studies in which brothers, and monozygotic and dizygotic twins were compared (Bouchard *et al*., 1986). The heritability for gains in aerobic capacity elicited during these studies have previously been reported to be estimated in the region of ~50% (Bouchard *et al*., 1999, Bouchard *et al*., 2000, Bouchard & Rankinen, 2001). However, while various polymorphisms are reported to be associated with a phenotype increase, they account, individually, for only a small proportion of the observed inter-individual variation in response to exercise training when added to a working model for $\dot{V}O_2$max trainability (Sarzynski et al., 2017).

2.4.2 Inter-Individual Variability of Maximal Oxygen Uptake in Response to Exercise

It has been suggested that training studies consistently report a high variability in the effects of regular exercise training (Hecksteden *et al*., 2018). While many phenotypes have been investigated, $\dot{V}O_2$max response has often been a focus for studies investigating claims of inter-individual variation in response to exercise. Wide inter-individual differences in the trainability of the cardiorespiratory system have been claimed for over 30 years (Lortie *et al*., 1984, Bouchard, 1995, Feitosa *et al*.,2002). Individual differences in the response to standardized regular aerobic exercise, measured as $\dot{V}O_2$max, have been reported in several studies in healthy subjects (Lortie *et al*., 1984, Bouchard & Rankinen, 2001), in which mean changes ranged from 10-15%, but inter-individual variation in response was reported to range from no change to 40% (Bouchard, 1995, Bouchard & Rankinen, 2001, Hautala *et al*., 2003, Hautala *et al*., 2006). However, such variation is consistent with the fact that biochemical and physiological functions vary in all humans (Vollaard *et al*., 2009). Nevertheless, these studies almost exclusively lack the crucial comparator sample, with which to make formal comparison of the SD_{change}, or disregard the data from such, therefore limiting the inferences that can be drawn from the pre-post single group trials. Those that have included a comparator sample (Prud'homme *et al*., 1984) have been shown to actually present more variation in the control sample, in comparison to the intervention (Williamson *et al*., 2017). Given these aforementioned claims of genetic background contributing to observed variation in

$\dot{V}O_2$max, it has recently been conceded that no specific genetic factors have been identified that explain the differential response to exercise (Vellers *et al*., 2018).

2.4.2.1 Initial Claims

Several formative studies on this topic were conducted in the 1980s, with the aim of identifying the inter-individual response to exercise. A further aim was to elucidate genotype dependency of the inter-individual variation in response (Prud'homme *et al*., 1984, Despres *et al*., 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Bouchard *et al*., 1986, Hamel *et al*., 1986, Simoneau *et al*., 1986). These studies are discussed at length in Chapter 3.

2.4.2.2 Physiological and Molecular Factors at Play?

A recent review (Sparks, 2017) sought to provide insight into the physiological and molecular factors surrounding the inter-individual variation in response to exercise interventions and provide insight into some of the statistical issues in this area. However, several inaccuracies can be identified, and these factors are crucial for answering the fundamental question of whether there are 'true' and clinically important individual differences in the response to exercise.

'True' inter-individual differences in response can be defined as inter-individual variations in response that are not merely random trial-to-trial variability. Instead, changes must be free of measurement error and random trial-to-trial within-subjects' variability, and then anchored to a rational and justified threshold for the minimal clinically important difference (MCID). It is also maintained that, in the 'roadmap' for researching this topic, true and clinically relevant individual response differences should be confirmed empirically before any putative moderators and mediators of the exercise response are explored (Atkinson & Batterham, 2015). The definition of 'non-response' given by these authors as "the lack of a difference between a control and a treatment condition with respect to a specific variable" (Sparks, 2017) raises concern, as it implies that non-responders can be identified by observing their data from a two-condition (control and exercise) experiment and concluding that those with a treatment-control difference of zero or less are 'non-responders'. The fallacy of this approach has been alluded to (Barker & Schofield, 2008), and a full account

of the pitfalls in non-responder identification has previously been provided (Atkinson & Batterham, 2015, Schubert *et al*., 2014).

The observed response comprises the 'true' response in addition random trial-to-trial within-subjects' variability and measurement error (Atkinson & Batterham, 2015). Therefore, observed non-response to exercise does not automatically mean that there has been a true non-response. Random variability in biological measurements from day-to-day or week–to-week is always present. It is, unfortunately, also essentially uncontrollable. This component of variance on its own often appears to provide evidence of inter-individual variation in exercise response, when in reality this is not the case.

The optimal approach for quantifying individual response differences in repeated trial studies has previously been described (Senn *et al*., 2011). This replicate crossover design involves control and exercise conditions that are both administered at least twice to each participant, usually in a balanced randomised sequence. Using this approach allows the exercise/control x participant interaction term to be derived from the statistical model (Senn *et al*., 2011), however this methodology can only be employed for acute exercise interventions and creates an increased burden on participants. This is an approach that had not been utilised in the exercise sciences until the proof-of-concept reported in Chapter 6.

2.4.2.3 The METAPREDICT Study

A recent multi-centre RCT focused on the evaluation of a new time-efficient and genuinely practical high-intensity interval training (HIIT) protocol in men and women with pre-existing risk factors for type 2 diabetes in the METAPREDICT study (Phillips *et al*., 2017), wherein participants were randomised to one of two interventions or a control group.

Intervention groups comprised of 7 by 1 (*n*=31) undertaking three cycling sessions per week for 6 weeks (2-min warm-up at 50 W followed by seven sets of 1-min high-intensity cycling work with 90 s recovery between sets), 5 by 1 (*n*=129), (2-min warm-up at 50 W followed by five sets of 1 min high-intensity cycling work with 90

s recovery between sets), or a comparator group (*n*=11), which was described as "serving to complement the short-term test–retest variability data collected in the intervention groups at the two baseline sessions with "test–retest" data covering the full duration of the study".

Participants who showed responses large enough to surpass certain thresholds were presented, in addition to the use of a regression model to describe the association between measurements made at baseline and the magnitude of response. A comparison of each individual is presented, with a range of apparent 'true' responses; however, this is absent the range of responses from the comparator sample. It has previously been described how this approach fails to accurately quantify the presence of 'true' inter-individual variation in intervention response (Hopkins, 2015, Atkinson and Batterham, 2015). It is noted that this approach is alluded to in the 'Data Processing and Statistical Analysis' section of the study. However, the use of a paired *t* test to further describe *p* values for a test of statistical significance is questioned; given these SDs are a single value, and not paired; this approach is not grounded in statistical rigour, and within-group paired *t*-tests were used in intervention(s) and control. This is bad practice in any analysis of trial data. Additional questions regarding the authors inferences are presented when considering that baseline data were not corrected for in analysis, where the use of ANCOVA is preferential, in order to identify differences at baseline which may account for any observed inter-individual variation.

These control data are reported to be either baseline 7-day variability data (*n*=201) OR control data (*n*=11). Weighting of control data is obviously on the 7-day reliability data, as only 6.5% of the control 'cases' were the comparator group measured at the same baseline and follow-up (6 weeks). These data are also likely to be associated with less within-subjects variability than that collected over the same time frame as the intervention, leading to false impressions of individual variance. There were substantially fewer subjects in the control sample, and this sample was not even used in the analysis of group mean differences.

Whilst a meta-analysis is also reported to have been undertaken, involving comparisons of SD_{change} with another SD_{change} from a previously published study,

these SDs were compared with a Levene's test rather than the recently presented calculation for quantification of inter-individual variation in response (Hopkins, 2015). By definition, this cannot be deemed a true meta-analysis, nor appropriate comparison of 'true' inter-individual variation in response.

2.4.2.4 Sprint Interval Training and Inter-Individual Variation in Response

When comparing sprint interval training (SIT) with traditional endurance training, it was recently observed that a prevalence of 22% of individuals were 'non-responders' to high intensity training protocols (Gurd *et al*., 2016). However, this combination study reported on several investigations that were also lacking a control group with which to compare intervention data. In addition, use of the previously described and problematic use of 2 x TE as a threshold for 'non-response' limit the inferences drawn from these findings. Similar findings of variability in magnitude of response were reported following a crossover study comparing the adaptive response of SIT and endurance training (Bonafiglia *et al*., 2016), however, it has been discussed how crossover studies of this design are not without their own limitations, due to unknown washout periods (Williamson *et al*., 2017). Whilst some authors have claimed up to 55% of participants showed no improvements in $\dot{V}O_2$peak (Bakker *et al*., 2017), a lack of comparator sample and low adherence to the exercise intervention cast doubts upon these findings.

Contrastingly, reduced prevalence of 'non-response' was also reported following high-volume interval training when compared to low volume SIT (Astorino & Schubert, 2014), but use of changes greater than the CV to define response limit these findings, given the lack of comparator sample and exclusion of random measurement error from the observed change.

2.4.3 Quantifying Inter-Individual Variation in $\dot{V}O_2$max Response to Exercise – A Summary

It is clear that concerns raised in regard to the methodological approach of much of the body previous research have foundation (Hopkins, 2015, Atkinson & Batterham, 2015, Williamson *et al*., 2017). As is emphasised throughout this thesis, the

identification of factors that may explain inter-individual response variance should come only after true, substantial inter-individual differences in response have been demonstrated and quantified properly (Atkinson & Batterham, 2015, Williamson *et al*., 2017). This quantification requires an appropriate control/ comparator group, preferably within a randomised trial design. However, it is evident that much of the published literature claims substantial treatment response heterogeneity based on analyses of changes in outcome in a single intervention group with no inclusion of a comparator sample in the research design, which would provide the required counterfactual (Williamson *et al*., 2017).

2.5 Energy Balance and Body Weight

Weight loss is a complex trait, depending upon multifactorial influences such as environmental, behavioural, and genetic factors (Deram & Villares, 2009). Indeed, bodyweight regulation also been hypothesized to be dependent upon the axis of food intake, body fat stores, nutrient turnover, and thermogenesis (Martinez & Fruhbeck, 1996, Jequier & Teppy, 1999), whilst also being dependent upon activity levels (Dokken *et al*., 2007)

Current assumptions focus upon the genetic background and dietary and activity habits (Martinez, 2000), such as habitual consumption of a high-fat diet being associated with obesity. However, some individuals have followed identical diets and remained lean (Macdiarmid *et al*., 1996). Diet, aerobic exercise, and a combination of the two have previously been reported to be successful in producing clinically worthwhile (>5%) bodyweight reduction (Donato *et al*. 1998), although conversely it has been suggested that many studies fail to prescribe sufficient exercise intensity, frequency, or duration to produce significant weight loss and subsequently provide no benefit over diet only interventions (Washburn *et al*., 2014).

Although it has been a heavily promoted public health approach to combat obesity, the role of exercise in weight management has previously been questioned. Exercise has beneficial effects on all-cause mortality and cardiovascular disease risk well above those interventions including nutritional interventions or supplementation (Fiuza-Luces *et al*., 2013). While it is generally accepted that exercise is an

important factor in weight loss, its exact role in the mechanism of weight control is still unclear (Myers *et al*., 2014).

The effect of aerobic exercise without dietary restriction on body mass has been reported to elicit reductions, with losses of 1.5-3.0 kg typically reported over 3-18 months (Shaw *et al.,* 2006). However, these findings must be taken with caution, due to variety in study design, unsupervised exercise and self-reported adherence.

Greater reductions in body mass have been reported under controlled (often laboratory) conditions when the exercise energy expenditure is larger (>2,000 kcal/week), or when exercise is combined with dietary restriction (Ross *et al.,* 2000), highlighting the importance of distinguishing between efficacy (the ability to bring about intended change under ideal conditions) and effectiveness (the extent to which change is achieved under 'real world' conditions). Regular aerobic exercise may be efficacious for weight loss under controlled conditions, but it may not be effective in the real world (due to poor adherence). This issue is explored further in Chapter 4.

2.5.1 Genetics and Body Weight

Given the prevalence of overweight and obesity, it is no surprise that efforts have been made to utilise high-tech approaches to elicit answers (Cauldfield, 2015). It has been suggested that genetic factors may contribute to some of the observed variation in body fatness (Bouchard *et al*., 1985, Stunkard *et al*., 1986a, Stunkard *et al*., 1986b, Barsh *et al*., 2000, Martinez, 2000, Marti *et al*., 2004), and weight loss in response to dietary and surgical interventions (Kovolou *et al*., 2016, Resende *et al*., 2018), with the FTO gene being the most predictive (Loos, 2012). However, even this gene is only associated with a modest amount of increased body fatness. It has been claimed that moderate to high heritability for obesity has been observed in family, twin, and adoption studies (Hinney at el., 2010). Between 25-70% of variation was reported to be hereditary in twin studies (Bouchard *et al*., 1985, Cardon *et al*., 1994), although lower figures of 25-50% in family studies have previously been reported (Stunkard *et al*., 1986a, Stunkard *et al*., 1986b). However, other data generally do not support these claims, primarily underpinning the notion that genetic associations generally have small effect sizes in 'precision medicine' interventions (Khoury & Galea, 2016). Indeed, all genomic markers identified have

only shown very small effects on both BMI and the risk of obesity (Tan *et al*., 2014). Given these findings, identification of a highly predictive obesity gene or even a set of genes has remained elusive. Considering this, monogenic causes of obesity are, actually, rare (Ells *et al*., 2018), and it has been stated that decreased physical activity is more likely to be the major contributing factor (Hill & Melanson, 1999), with environmental factors likely affecting lifestyle choices, though the search for a 'obesity gene' continues (Whalley *et al*., 2009). The idea that we can blame genetics for obesity is clearly flawed, as our genes are relatively unchanged for thousands of years, whereas obesity prevalence has increased dramatically only recently. Rather, it is likely environmental factors that provide a substantial contribution.

2.5.2 Inter-Individual Variability in Body Weight Response to Exercise

The concept of 'personalized medicine' in relation to the treatment of obesity has been suggested to use genetic information to inform diet, exercise, and other weight loss strategies (Agurs-Collins *et al*., 2008). Inter-individual variation in fat loss and weight loss in response to exercise has previously been reported (Snyder *et al*., 1997, Byrne *et al*., 2006, King *et al*., 2008, Caudwell *et al*., 2009, Church *et al*., 2009, Barwell *et al*., 2009), resulting in a prevailing opinion that exercise often results in less than expected weight loss (Donnelly & Smith, 2005). However, in a similar approach to those studies previously discussed, these inferences are almost exclusively drawn from studies lacking a control group.

An early study investigating chronic energy deficit in twins elicited by exercise, over a four-month period, postulated the presence of large individual differences in weight loss (Bouchard *et al*., 1994). These findings were presented in conjunction with data indicating greater heterogeneity between twin pairs than within pairs. However, it has previously been discussed how this approach may overestimate heritability (Heller *et al*., 1993) and does not separate genetic from environmental pathways (Maes *et al*., 1997).

2.5.2.1 Gender Based Differences in Response

Sex differences in exercise-mediated weight change have been reported (Ballor & Keesey, 1991, Donnelly & Smith, 2005), possibly due to exercise-induced EI suppression in males (Hall *et al*., 2011, Caudwell *et al*., 2012), compensatory eating (Finlayson *et al*., 2009, Unick *et al*., 2010, Melanson *et al*., 2013, Hopkins *et al*., 2014), and exercise intensity below that prescribed (Doucet *et al*., 1999). However, differences in methods between studies causes problems in interpretation. It has been cited that the reason for a sex difference is that women are better at defending body weight and will therefore increase EI in response to EE. However, a recent systematic review found this not to be the case (Caudwell *et al*., 2014), with a lack of robust evidence demonstrating increased compensatory EI in women. In the HERITAGE Family Study, men were reported to lose more weight than women and children, and more fat than women, but no other gender differences were observed (Wilmore *et al*., 1999). Overall, in studies with no control sample, evidence for a sex effect on inter-individual variation in response to exercise in short-, medium-, and long-term exercise trials is weak (Caudwell *et al*., 2014).

When exercise is matched, and EE is controlled, measured, and the same for both sexes, similar changes are observed for weight loss (McTiernan *et al*., 2007, King *et al*., 2010, Donnelly *et al*., 2013, Caudwell *et al*., 2012, Caudwell *et al*., 2014), appetite suppression, and hormone regulation (Hagobian & Braun, 2010), though large inter-individual variation in exercise-induced weight loss is still reported (Caudwell *et al*., 2012). Again, these studies are lacking a control sample; therefore, knowledge of the counterfactual is absent and these data should be interpreted with caution. When a control sample is included, although not analysed in direct comparison to the intervention, similar variation is observed in all conditions (e.g. Church *et al*., 2009), (Fig. 1.).

2.5.2.2 Other Suggested Mechanisms

Differences in the response of weight loss among individuals have been reportedly linked to variability in diet make-up (Senior *et al*., 2016), baseline respiratory quotient (the ratio of fat to carbohydrate oxidation). These findings may indicate that

fat oxidation or the ability to increase fat oxidation in response to changes in energy intake may affect individual weight loss (Barwell *et al*., 2009).

Inter-individual variability in weight loss following an exercise intervention has also been attributed to sex-based differences in appetite hormones (Hagobain *et al*., 2008, Hagobian *et al*., 2009, Hagobian & Braun, 2010) and the compliance with the intervention (Manninen *et al*., 1998, Bruce *et al*., 2003). However, even with near perfect compliance, underlying compensatory responses may also affect energy balance (King *et al*., 2008), while in children, sex, age and baseline body fat, diet have been postulated to be possible mechanisms (Barbeau *et al*., 1999).

For some, exercise is an unsuccessful method of weight control (King *et al*., 2008), possibly due to compensatory behaviours counteracting the benefits of exercise (King *et al*., 2007a, Finlayson *et al*., 2009, Rosenkilde *et al*., 2012), but as the longer-term habitual day-to-day variability in EI and EE is as yet unclear (Stubbs *et al*., 2004), the certainty of this belief could be questioned.

Compensatory adaptive mechanisms opposing negative energy balance (Stubbs *et al*. 2004) such as reduced metabolic rate or increased appetite (Rosendilke *et al*., 2012), reductions in energy expended during spontaneous exercise (Goran & Poehlman, 1992) and partial EI compensation (Blundell *et al*., 2003, Hopkins *et al*., 2014) have previously been noted; immediate compensatory increases in EI in response to EE have recently been rejected (Hopkins *et al*., 2016) but persisting with exercise may drive increased EI (Stubbs *et al*., 2002a, Stubbs *et al*., 2002b, Whybrow *et al*., 2008).

Evidence has been offered of increased motivation to eat following longer-term energy deficit (Heini *et al*., 1998, Drapeau *et al*., 2007, King *et al*., 2007b). To investigate this phenomenon, 35 overweight and obese participants undertook 12 weeks of exercise eliciting 500 kcal EE per session, 5 times per week (King *et al*., 2008). While wide variability in weight (-14.7 to +1.7 kg) and fat (-9.5 to +2.6 kg) changes were reported, linked to metabolic and/or behavioural adjustments, no control sample was included. This key omission renders analysis of the spread of change inaccurate, due to the lack of presentation of the standard deviation of the change score for intervention vs control. Classification of ‘responders’ and ‘non-

responders' dependent upon achieving prior weight loss targets is also an unsuitable approach for quantifying the inter-individual variation in response.

2.6 Blood Pressure and the Effects of Exercise

Blood pressure is the product of cardiac output and total peripheral resistance (Sabbahi *et al*., 2018). High blood pressure is a serious public health challenge (Wolz *et al*., 2000), given that it affects 25% of the world's population (Carpio-Rivera *et al*., 2015). There is an association between blood pressure and all-cause and cardiovascular mortality. According to the WHO Global Burden of Disease report, high blood pressure is the leading single risk factor for global burden of disease (Lim *et al*., 2012), although that is now challenged by diseases such as diabetes (WHO, 2016), which contributed to over 1.5 million deaths in 2012.

2.6.1 Blood Pressure Reactivity

Acute psychological or physiological stress is associated with factors that explain a number of cardiovascular related comorbidities, such as endothelial dysfunction, oxidative stress, the development of atherosclerosis and inflammatory reactivity (Huang *et al*., 2013). Although an increase in blood pressure is expected and a normal physiological response to exercise (Yzaguirre *et al*., 2017), it is hypothesized that the magnitude of cardiovascular reaction to stress is related to future blood pressure status and cardiovascular disease (Carroll *et al*., 2011), with greater reactivity predicting poor cardiovascular outcomes. An exaggerated systolic blood pressure response of more than 180 mmHg during moderate submaximal exercise or diastolic blood pressure of more than 95 mmHg during maximal exercise has been suggested to be the best predictor of new-onset hypertension at 20 year follow up (Yzaguirre *et al*., 2017).

There is currently little empirical research into the inter-individual variation in blood pressure in response to exercise. However, it has been reported that males and females, whilst utilising the same pathways for stress response, appear to do so with a variation in results (Huang *et al*., 2013). Males often present larger chronic

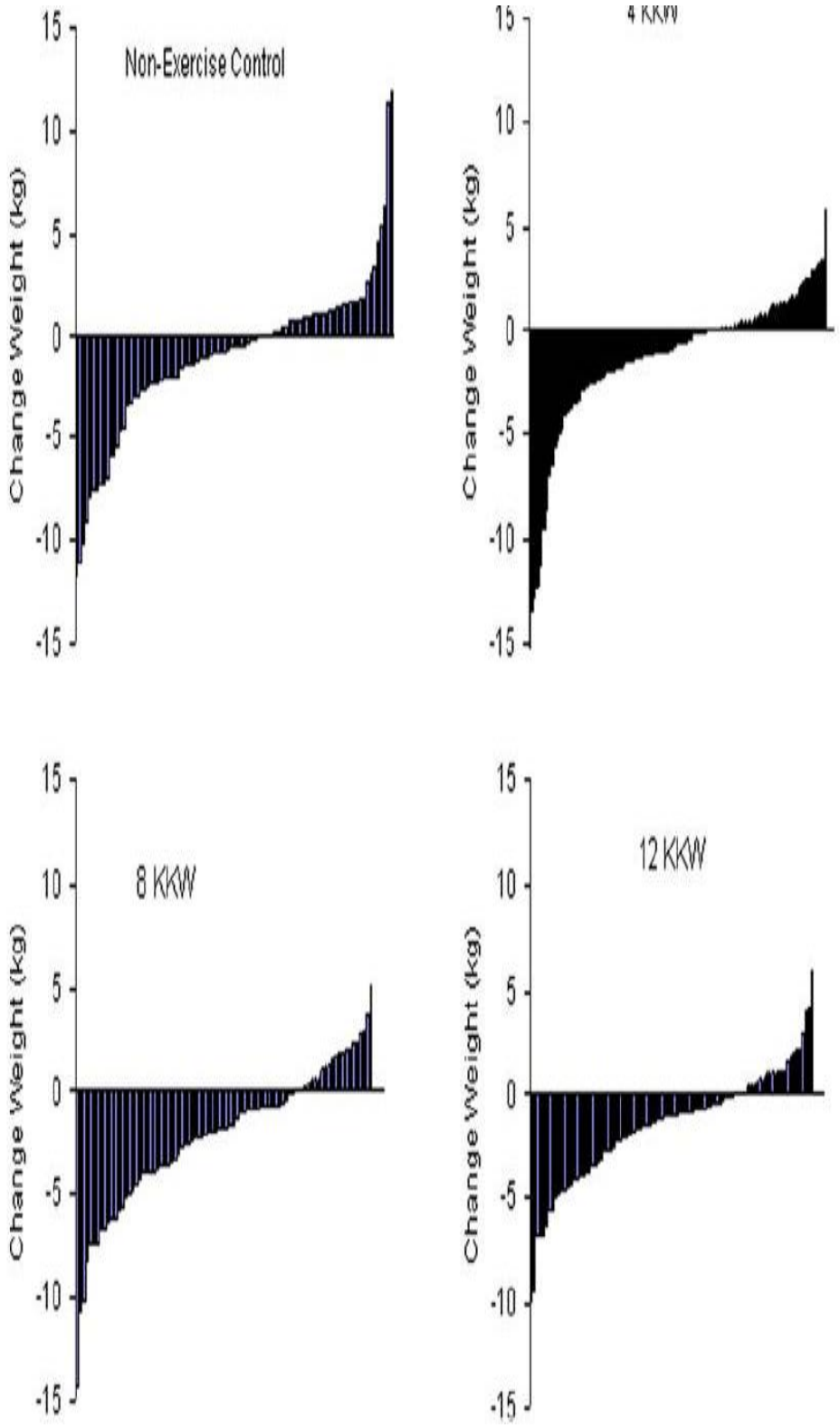

Fig. 1. Comparison of individual variation in response to exercise, showing similar responses in control sample (Church et al., 2009).

2.6.1.1 Mechanisms for Gender Differences

diastolic blood pressure responses to acute exercise. This observation supports the notion that that male responses are 'vascular' while female responses are 'cardiac' (Allen *et al*., 1993), though this has recently been countered with reports of continued diastolic increase throughout life in both sexes. Whereas males show consistently greater SBP and DBP until the sixth decade before a plateau in DBP by the seventh, female peak DBP appears to catch up with, and surpass, that of males (Sabbahi *et al*., 2018). Given cardiac output decreases with age, it may be that a blunted vasodilatory response to exercise in females is responsible for this shift in DBP (Sabbahi *et al*., 2018). Whilst these suggestions may explain chronic changes and may be as a result of the 'last bout' effect (Plowman & Smith, 2007), no published research is available regarding the acute inter-individual variation in blood pressure response to exercise. These outcome measures are addressed in Chapter 5 (chronic blood pressure change) and Chapter 6 (acute blood pressure response to high intensity aerobic exercise) of this thesis.

2.6.2 Heart Rate Response

Individuals with higher fitness levels appear to present a smaller magnitude of heart rate reactivity response (Boutcher & Nugent, 1993), though the mechanisms are not explicitly known at this time (Lambiase *et al*., 2013). Potential explanations may come from the fact that exercise elicits noradrenaline release in a curvilinear manner in response to increased workload and in combination with adrenaline (Rowell & Shepherd, 1996) may be responsible for the magnitude of observed rise in exercise heart rate and blood pressure.

2.6.3 Inter-Individual Variability of Blood Pressure and Heart Rate in Response to Exercise

Little published evidence has alluded to the inter-individual variation in the response of blood pressure to either acute or chronic exercise. In a short study investigating the individual blood pressure response of 13 participants with peripheral arterial disease, it was reported that only 8 patients had increases of greater than 4 mmHg in at least one of two exercise (aerobic or resistance training) sessions (Lima *et al*.,

2015), suggesting a range of responses to the intervention. The mixture of medication taken by participants adds a confounding variable not controlled for in analysis.

It was recently suggested that while exercise may benefit the majority, blood pressure adaptation may be heterogeneous in nature (Chen, 2010, Loenneke *et al*., 2014), although this has been refuted, with a suggestion that the findings were the result of contamination by the regression to the mean statistical artefact (Atkinson & Taylor, 2011, Atkinson, 2015). Re-analysis of HERITAGE Family Study data was also claimed to show 12.2% of the sample presenting adverse resting SBP response to exercise (Bouchard *et al*., 2012). It has been proposed that these variations in response are associated with gene polymorphisms (Mori *et al*., 2009). Those with angiotensin-converting enzyme (ACE), apolipoprotein E (apoE), and lipoprotein lipase (LPL) genotype variants (Hagberg *et al*., 1999) are likely positive responders to exercise, possibly due to the role the renin-angiotensin system plays in the regulation of blood pressure. A more recent genome-wide association study also suggests thirty loci are responsible for heart rate response to exercise (Ramirez *et al*., 2018); however, it is unknown whether these findings would hold true if the individuals identified were exercised in an RCT-style intervention. There is currently no empirical evidence regarding inter-individual variation in heart rate response to acute exercise. Given the lack of research in this area, it is clear that this is a critical physiological variable that has potential for deeper investigation.

2.7 True Inter-Individual Variability in Response to Exercise: Does it Exist?

Although decades of observations regarding inter-individual variability appear convincing, superficially, the conclusions of the previously mentioned studies assume that the variability in response for a trait is solely a consequence of exercise. However, the individual variability often attributed to the intervention group (treatment), can include numerous sources of variability such as measurement error, random (biological and measurement) variability, between-subject variability (if unadjusted for baseline), subject-by-treatment interaction and within-subject variability.

A summary of the potential sources of variability are given in Table 1. The subject-by treatment interaction, commonly known as the inter-individual variability in response to treatment, represents the variability in differences of training response between individuals. However, to adequately quantify the variability for the subject-by-treatment interaction, confounding sources of variability should be considered. In a parallel group RCT, we get the individual response variance by deduction. The variance of the changes in the control around the mean change are made up of between- (B) plus within-subjects (W) variance. The variance of the changes in the treatment arm is given by B+W+R, where R is the true individual response variance. Therefore, treatment minus control = (B+W+R) – (B + W) = R, by deduction, assuming that in an RCT B and W are the same between groups. Only a replicate crossover can fully partition the sources of variance, but that design may only be applied to acute effects.

For these reasons, the early studies describing individual response to exercise have been criticized by those who suggest that limitations in study design and analytical approach confound the interpretation of data and the inferences drawn (Hopkins, 2015, Hecksteden *et al*., 2015, Atkinson & Batterham, 2015, Williamson *et al*., 2017). Of primary concern, from a design perspective, is that these early studies did not include a control group, and consequently could not account for the random variability over time for the trait under study.

Furthermore, despite inclusion of a control group in some study designs, many authors did not consider incorporating the control group data in their analysis (Prud'homme *et al*., 1984, Sisson *et al*., 2009, Church *et al*., 2009, Ross *et al*., 2015); therefore the 'true' variability in response is not adequately quantified.

2.8 Gaps in the Literature and Rationale for Further Research

Much attention has been given to the notion of individual responses, but it is clear that several common limitations can be identified within many of the studies investigating the inter-individual variation in response to an exercise intervention. Almost exclusively in these studies, a control group is either absent or discarded in the data analysis. As highlighted, the inclusion of data from a comparator group to compare the inter-individual response to the given intervention is of principal

importance and has previously been emphasised (Atkinson & Batterham, 2015). Without this, the resultant data analysis is largely inaccurate and potentially misleading (Atkinson & Batterham, 2015), with measurement error and random or biological variation in response to an intervention mistaken for true individual differences in response (Leifer *et al*., 2015). Plots of individual differences in the baseline-to-follow up change are often presented for the exercise training study arm only (Sparks, 2017). Yet a very similar graph can usually be plotted for the baseline-to-follow up change in the control group. This has been observed (Church *et al*., 2009, Songsorn *et al*., 2016), but the resultant analysis of the control sample is often lacking.

In an RCT, true individual differences in exercise response are present only if the SD of change is substantially larger in the exercise group than the control group. If not, the apparent individual differences in 'response' are nothing but baseline-to-follow up within-subjects' variability, which can be large if there are many weeks (>6) between baseline and follow up in the study. This observation is common in most studies. In a critical review of a selected sample of exercise training studies with $\dot{V}O_2$max as the outcome, it was identified that very few studies included data from a control group in their analyses. For those studies that had a control group, there was little evidence that the difference in the SD of changes between intervention and control was clinically important, relative to an MCID of 1 MET (Williamson *et al*., 2017).

Determining whether there are true individual differences in the responses to exercise that are large enough to be clinically relevant is a crucial platform for precision medicine. If the individual differences in response are found to be not clinically important, the need to proceed to explore individual moderators and mediators of response is questioned, as such explorations could be wasteful in terms of participant time and funding money.

Little research has employed this key aspect of methodology required for the accurate quantification of inter-individual response. Despite many of the aforementioned studies' lack of comparator arm, they have provided the basis for a

Table 1. Potential sources of variability during exercise trials. Adapted from Bell et al., 2008.

Source of variability	Description	Ways to account for variability	Error
Random variability	Influences pre/post outcome values Comprised of: measurement error – the difference between the observed value and the 'true' value' biological variability – random fluctuations over time	Use $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$ to separate from subject-by-treatment variability	
Between treatment	The variation between treatments averaged over all patients	Parallel group trial	Between patient, Subject-by-treatment interaction, within treatment
Between-subject	The variation between patients given the same treatment True differences between individuals (i.e. baseline differences)	Include baseline as covariates	Subject-by-treatment interaction, within treatment
Subject-by-treatment interaction	'True' inter-individual variation in response due to treatment/intervention The extent to which the effects of the treatment vary from patient to patient	Use $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$ to properly separate from random variability in a chronic training study. Utilize replicate crossover for acute effects	
Within subject	Reproducibility of training effects Magnitude of change within same subject Variation from occasion to occasion when patient is given the same treatment	Use replicate crossover method Allows for partitioning of period effect	

growing body of work. Indeed, from the investigations that informed and framed the implementation of HERITAGE, only one (Prud'Homme *et al*., 1984) actually included a control group, and even then, more variability was observed in the control sample vs the intervention (Williamson *et al*., 2017).

Not all inter-individual response may be due to these aforementioned factors. Neither does it confirm that this assumption of inter-individual difference in response is true for any particular study (Atkinson & Batterham, 2015). Small day-to-day changes cannot be classified as a worthwhile change, and the response must be clinically relevant and more than the natural biological variation between baseline and follow-up measurements (Scharhag-Rosenberger *et al*., 2012). Of course, patients differ not only by genetics, but also by their personal history and environmental circumstances (Senn, 2001), and this can lead to a multitude of effects on individual response. There appears to be little doubt that the response to exercise training is influenced by multiple factors, including those not discussed herein, such as psychosocial and environmental.

The variability in the changes in an intervention group must be assessed against the backdrop of this natural variability. In an RCT, the mean effect of the intervention is given by the mean change in the intervention minus the mean change in the control. This logic should be extended to the assessment of individual responses.

Therefore, the primary aim of this programme of work is to quantify the clinically relevant inter-individual differences in the response to exercise training once appropriate data analysis approaches are employed. It is evident that further research is required to quantify 'true' inter-individual variation in response to exercise interventions. If such variation is present, and represents a clinically meaningful difference, identification of potential moderators and mediators would be of great value to the personalization of exercise prescription. This research is important if we are to understand the nature of 'true' inter-individual response to exercise, and to further investigate the moderators and mediators of this heterogeneity of response.

Chapter 3: Inter-Individual Responses of Maximal Oxygen Uptake to Exercise Training: A Critical Review

3.1 Preface

Given the review of the literature presented in Chapter 2, it is important that a deeper, more critical review is undertaken in order to understand, and re-analyse, previously published literature purporting to show inter-individual variation in the response of maximal aerobic capacity to chronic exercise interventions. This chapter takes a contructively critical view of much of the published literature, but also makes the point that this area is critical for understanding the reasoning for employing a robust approach to the quantification of inter-individual variation in response. This chapter is based upon a peer-reviewed research paper, published in *Sports Medicine* in (Williamson *et al*., 2017).

3.2 Introduction

Interest in the concept of individualised responses to an intervention as part of 'personalised medicine' and 'precision care' has been growing over the last 30 years (Prud'homme *et al*., 1984, Despres *et al*., 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Hamel *et al*., 1986, Simoneau *et al*., 1986, Rose & Parfitt, 2007, Senn *et al*., 2011, Bouchard, 2012a, Mann *et al*., 2014, Bouchard *et al*., 2015). In pharmacogenetics, there has been particular interest in 'tailor-made' drugs and therapies, based on the individual response of a patient and/or certain moderators and mediators of that response (Spear *et al*., 2001, Senn *et al*., 2011). Personalised medicine has also been considered in the context of inter-individual differences in the response of health outcomes to various exercise interventions.

It has been highlighted that the majority of researchers focus upon 'main effects' and mean group changes (Bouchard & Rankinen, 2001). These statistics are useful, but do not allow us to distinguish between cases (Senn, 2004), may hide a wide range of responses (Karavirta *et al*., 2011) and have previously been described as misleading (Bouchard, 1983, Bouchard & Rankinen, 2001). True inter-individual differences in

the response to an intervention are less frequently reported, even though it has been proposed that there is large inter-individual variability in response to physical activity interventions (Prud'homme *et al*., 1984, Despres *et al*., 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Hamel *et al*., 1986, Simoneau *et al*., 1986, Bouchard & Rankinen, 2001, Hautala *et al*., 2003)

Importantly, even in the studies in which inter-individual differences in the response to exercise training are considered, concerns have been levelled at the designs and analytical approaches in these studies (Hopkins, 2015, Atkinson & Batterham, 2015). Therefore, it is important at this time for the claims of inter-individual differences in response to an exercise intervention, with a particular focus on maximal oxygen uptake ($\dot{V}O_2max$), to be scrutinised in the context of these recent criticisms. Consequently, I undertook this critical review on the HEalth, RIsk factors, exercise Training And GEnetics (HERITAGE) Family Study, as well as the studies that preceded it and the more recently published research. I will focus especially on any apparent limitations of previously adopted data analysis approaches, and how researchers have investigated potential moderators and mediators of the inter-individual difference in $\dot{V}O_2max$ response to an exercise intervention. Finally, I present what I consider to be an appropriate trial design and analysis approach in order to quantify true inter-individual differences in $\dot{V}O_2max$ response to exercise interventions. My focus in this regard is on parallel group randomised controlled trials, as I believe that this design is more widely applicable to research questions addressing chronic adaptations to training. Moreover, published chronic training studies with $\dot{V}O_2max$ as the outcome are exclusively before-and-after designs, either with or without a control group, with a single intervention period. However, it is acknowledged that other designs and statistical approaches have been proposed for quantifying individual differences in response to treatments, primarily the multiperiod (replicate) crossover design (Hecksteden *et al*., 2015, Senn, 2016).

3.3 Maximal Oxygen Uptake and Precision Medicine

Low cardiorespiratory fitness has been established as an independent predictor of all-cause mortality and cardiovascular disease (Laukkanen *et al*., 2004, Sui *et al*., 2007). Many researchers have highlighted the favourable changes in risk factors that occur

following a period of exercise training (Myers *et al*., 2002, Church *et al*., 2007, Kelley & Kelley, 2008, Church *et al*., 2010). Given that one metabolic equivalent (MET) is the amount of oxygen consumed whilst sitting at rest, and is ≈3.5 $mL.kg^{-1}.min^{-1}$ (Jette *et al*., 1990), research that 1-MET increase in cardiorespiratory fitness translates to a 12% reduction in cardiovascular disease and all-cause mortality risk has been reported (Myers *et al*., 2002).

While a multitude of phenotypes have been investigated, $\dot{V}O_2max$ response has often been the focus for authors observing the inter-individual variation in response to exercise. Wide inter-individual differences in the trainability of the cardiorespiratory system have been claimed (Lortie *et al*., 1984, Bouchard, 1995, Feitosa *et al*., 2002), with reports that the improvements in $\dot{V}O_2max$ range from zero to a 40% increase (Bouchard, 1995). Such variation is consistent with the fact that biochemical and physiological functions vary in all humans (Vollard *et al*., 2009). Several researchers have also reported that some individuals show little or no improvement in markers such as lipolytic activity, insulin sensitivity, maximal work rate, submaximal exercise heart rate and respiratory exchange rate following an exercise intervention (Despres *et al*., 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Hamel *et al*., 1986, Simoneau *et al*., 1986). Conversely, it has been proposed that physical activity may increase cardiovascular risk in some individuals, worsening risk factors beyond measurement error and biological variation (Bouchard *et al*., 2012b), although this notion is not consistent with the results of a more recent study, based upon the cardiovascular markers monitored (Leifer *et al*., 2015), although differences in thresholds for adverse response between these studies limit the comparisons that can be drawn.

Prescription of exercise is often undertaken with a global approach rather than a personalised one, and as exercise interventions are often utilized to reduce or prevent age-related reduction in function or lifestyle related diseases, attention should be paid to the response of each participant within a study (Kainulainen, 2009). If an individual is likely to respond favourably to a given stimulus, he/she is more likely to engage with that mode of exercise. Consequently, identifying individuals likely to gain greatest benefit would allow practitioners to also focus on alternative exercise,

dietary or pharmacological options for those that may be less likely to respond (Rankinen *et al*., 2010, Timmons *et al*., 2010).

3.4 A Critical Review of the Relevant Studies

Via a search of the relevant literature databases, I aimed to locate all the studies in which inter-individual differences in the response of $\dot{V}O_2max$ to an exercise intervention have been considered. I was particularly interested in ascertaining how many of these studies incorporated a relevant comparator sample into their design. Data from this sample have been deemed to be important for precise quantification and interpretation of inter-individual differences in response (Hopkins, 2015, Atkinson & Batterham, 2015). Without these data, measurement error and random or biological variation in the study outcome over time can compromise the quantification of true inter-individual differences in response (Leifer *et al*., 2015). Importantly, any physiological outcome can show substantial natural variability over a 4-6-month follow-up period in a control sample that does not receive the intervention (Leifer *et al*., 2015). This variation will also be present in the intervention group, irrespective of the additional influence of the intervention itself.

3.4.1 Pre-HERITAGE Studies

The seminal studies on this topic were conducted in the 1980s, with the aim of identifying the inter-individual response to exercise and to clarify the genotype dependency of the modulation of response (Prud'homme *et al*., 1984, Despres *et al*., 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Hamel *et al*., 1986, Simoneau *et al*., 1986) (Table 2). The effects of a 20-week endurance training programme on maximal aerobic power (MAP), ventilatory aerobic threshold and ventilatory anaerobic threshold in ten pairs of monozygotic twins were initially investigated (Prud'homme *et al*., 1984). Unlike in later studies, a comparator (no-exercise training) group was included in this study. From the intraclass correlations (ICC) reported, the authors described a highly variable response to training and concluded that sensitivity to training is genotype-dependent. The authors estimated that 20-25% of training-induced variation in MAP was due to within-pair differences.

Nevertheless, using the approach recently described (Atkinson & Batterham, 2015), re-analysis of the data presented in Table 1 of this study revealed that whist the mean changes were 5.5 mL.kg^{-1}.min^{-1} in the intervention and -0.6 mL.kg^{-1}.min^{-1} in the control, no clinically important differences in the SD of the change scores between the groups (control ± 5.6 mL.kg^{-1}.min^{-1}, intervention ± 3.7 mL.kg^{-1}.min^{-1}). This observation indicates that there are no substantial inter-individual differences in response to the intervention (Atkinson & Batterham, 2015). In fact, these SDs indicate greater variability in response in the control group versus the intervention group. It has been previously argued that this phenomenon may be due to imprecision in the estimation of inter-individual responses with inadequate sample sizes and/or caused by the intervention having a 'homogenizing' effect on the outcome variable, thus reducing the SD of the changes relative to the control group (Atkinson & Batterham, 2015).

The point estimate for the true individual response variability (SD_{IR}) for the above data is -4.2 (90% confidence interval, -6.3 to 2.0) mL.kg^{-1}.min^{-1} (calculated by $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$), with the negative point estimate indicating more response variability in control versus intervention. Note, however, that the upper limit of the 90% CI, which are calculated using the observed value (-4.2) plus or minus the standard error times 1.65 (Hopkins, 2015), for the SD_{IR} is 2 mL.kg^{-1}.min^{-1} (implying more variability in response in the intervention group). This indicates an 'homogenising' effect in the intervention sample. The SD_{IR} should be doubled before evaluating its magnitude to reflect a comparison between a typically high (mean + SD_{IR}) and typically low (mean – SD_{IR}) responder (Hopkins, 2015). Modelling the variances directly (quantifying the area under the curve for the distribution of SD_{IR} that is beyond 3.5 mL.kg^{-1}.min^{-1}), the probability that the true population effect for 2 x upper limit of the 90%CI of the SD_{IR} (4 mL.kg^{-1}.min^{-1}) is greater than the minimum clinically important difference (MCID) of 1 MET is only 6% (unlikely to be clinically important). This analysis shows that, even allowing for the uncertainty in the estimate of true individual response variability in small samples, the odds are stacked against meaningful inter-individual differences in the response of maximal oxygen uptake to exercise training.

Further research was undertaken (Despres *et al*., 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Hamel *et al*., 1986, Simoneau *et al*., 1986, Bouchard *et al*., 1986), with the study authors claiming there to be large variations in response to exercise for a number of phenotypes, including adipose tissue, fat cell weight, lipolytic activity, glucose conversion into fat cell, triglycerides, skinfolds, percentage body fat, anaerobic, alactic and lactic acid capabilities, fibre type, enzyme activity, sensitivity of muscle characteristics and aerobic endurance performance. Crucially, no comparator group was included in these studies.

A variation in improvement in maximal aerobic performance ($\dot{V}O_2$peak) of between 5 and 88% that was not correlated with a similarly wide range of 16-97% increases in total work output accomplished in a 90-minute ergocycle performance test was reported in one study (Lortie *et al*., 1984). Inter-individual responses were concluded following the observation of greater between-pair variation than within-pair variation in monozygotic twins, and through sex differences in those studies using mixed-sex cohorts (Despres *et al*., 1984). Genotype dependent responses for both maximal aerobic power and endurance performance were observed in conjunction with skeletal muscle enzyme changes following a fifteen-week training programme (Hamel *et al*., 1986), while inter-individual differences in anaerobic alactacid (ALC) and lactacid (AAC) response, fibre type changes and enzyme activity were reported in response to high intensity intermittent training (Simoneau *et al*., 1986). ALC and enzyme activity were said to be determined by genotype, although no such relationship was observed for other measured variables. The use of siblings was used to make inferences about the importance of genetic influence in heritability, with *F*-ratios suggesting 5-10 times more variance between twin pairs than within pairs. Similarly, genetic determination has been claimed for several different aerobic performance measures from the results of studies in which brothers, monozygotic and dizygotic twins were compared (Bouchard *et al*., 1986). Changes in aerobic fitness ranging from 0-58% were later reported among adults aged 60-71, where a trend for older participants improving less than younger subjects was observed (Kohrt *et al*., 1991).

The justification for the lack of a non-exercising control in the subsequent HERITAGE Family Study, which appears to have been continued through

subsequent investigations, was an observation of mean values from previously studied control groups remaining unchanged (Wilmore *et al*., 2001). However, a finding of no substantial change in the mean for the control group can occur in the face of substantial random within-subject variability in the changes in $\dot{V}O_2$max over the duration of the study. The variability in the changes in the intervention group must be assessed against the backdrop of this natural variability. In a randomised controlled trial (RCT), the mean effect of the intervention is given by the mean change in the intervention minus the mean change in the control. This logic should be extended to the assessment of inter-individual responses to an exercise intervention. In a parallel group RCT, one cannot say with 100% certainty whether or not any specific individual in the intervention group is a positive responder, as what would have happened to that person if, contrary to the fact, they had been in the control group is unknown. This is the fundamental counterfactual basis of the RCT, and whilst $\dot{V}O_2$max will not increase spontaneously, it may be impacted by changes in body mass in the absence of changes in absolute aerobic capacity. However, if the variance in the response in the intervention group is substantially greater than that in the control arm, then true individual responses may be inferred. The control group variability over the same time period as the intervention effectively provides our best guess of the counterfactual - what would have happened to individuals in the intervention group if they had been in the control arm. In parallel group RCTs, substantially greater response variance in the intervention group versus control is both necessary and sufficient for inferring true inter-individual differences in response to the intervention. Assuming that sample estimates are accurate estimates of the population values, it is incontrovertible that there must be a larger variance in response in intervention vs. control if true individual differences exist in response to treatment. Furthermore, although a parallel group RCT cannot isolate variance due to subject-by-treatment interaction (Senn, 2016), in this design a greater response variance in intervention vs. control is sufficient to infer inter-individual responses. As described, for any individual in the intervention arm we can then derive the probability of being a positive responder/ trivial responder/ or negative responder.

Table 2. Early studies presenting inter-individual response to exercise interventions.

		Exercise Training Program			Results	
Literature Citation	**Subjects/Groups**	**Mode**	**Length**	**Intensity/Frequency/Duration/Volume**	**Δ BW/ $\dot{V}O_2$ max/Lipids**	**Other**
Prud'Homme *et al.*, 1984	*n* = 48 (10 pr (6M, 4F) MZ twins & 14 (7M, 7F) control)	Cycling	20 wk	4-5d/wk; 40-45mins; 60-85% HRR	Variable response claims that sensitivity to training is genotype dependent	20-25% of training induced variation in MAP due to within-pair differences
Despres *et al*., 1984	*n* = 22 (11M, 11F)	Cycling	20 wk	4-5d/wk; 40mins; 80% MHR	No Δ in fat cell number. Δ fat cell weight. Δ lipolysis	Δ lipolysis response greater in males than females. Females had no Δ in fat mass, skinfolds. Increased MAP (SDs =6.8/6.9/4.2/2.9).
Lortie *et al*., 1984	*n* = 24 (13F, 11M)	Cycling	20 wk	4-5d/wk; 40-45mins; 60-85% HRR	Δ MAP/kg 33%; MAC/kg by 51%; Males Δ in MAC/kg 50% more than females.	Δ 5-88% MAP/kg & 16-97% in MAC/kg.
Savard *et al*., 1985	*n* = 24 (13F, 11M)	Cycling	20 wk	4-5d/wk; 40-45mins; 60-85% HRR	Δ Insulin stimulated glucose conversion to triglycerides Δ in males, but not females. Similar Δ in MAP.	Suggests Δ in modification of fat cell glucose metabolism.
Hamel *et al*., 1986	*n* = 12 (6 prs MZ twins)	Cycling	15 wks	15 wk, 3-5d/wk; 30-45mins; 60-85% HRR including 1/wk HIIT; 3x10mins; 80-85% with 5mins recovery	Δ in aerobic enzyme activity in wks 8-15. 5-10 x more variation	No fiber type Δ

					between than within pairs.	
Simoneau *et al*., 1986	*n* = 28 (14 pr monozygotic twins, (7M pr, 7F pr))	Cycling	15 wk	HIIT 10 x 15-30s & 4-5 x 60-90s,;HR recovery to 120-130b.min efforts; 4-5d/wk.	Δ T1 fibres, AAC, ALC, enzyme activity & T2 fibres.	Large interindividual differences, but similar within twin. Genotype suggested as responsible for responsiveness to HIIT on several variables. 65% of ALC associated with genotype. Δ oxidation following HIIT. Fibre type changes independent of genotype.

Δ change, BW body weight, pr pair, M male, F female, MZ monozygotic, wk week, mins minutes, MAP maximal aerobic power, MHR maximal heart rate, HRR heart rate reserve, MAC maximal aerobic capacity, HIIT high intensity interval training, T1 type 1, AAC lactacid, ALC anaerobic alactacid, T2 type 2.

3.4.2 Recent Studies

Six to nine times more variance in $\dot{V}O_2$max response between monozygotic twin pairs than within pairs has been reported (Bouchard *et al*., 2000). This and other studies were described as 'standardized and carefully monitored' (Bouchard, 2012a), with a 'careful and constant program of quality control and assurance' (Gagnon *et al*., 1996); yet still lack a suitable comparator sample. Nevertheless, RCTs are not only relevant to the investigation of main effects (Hecksteden *et al*., 2015). Use of the intervention-only arm as a basis for analysis is problematic, as similar or even greater variability of changes may also be observed in a control group, as was the case when a previous study was re-examined (Prud'homme *et al*., 1984). I fear that too much emphasis has been placed on gene relationship statistics without answering the initial and crucial question of whether clinically-relevant inter-individual differences in response exist. This question is answered by calculating the difference in baseline to follow-up variability between intervention and comparator groups and comparing this difference to a rationalised MCID (Atkinson & Batterham, 2015).

More recently, large variations in $\dot{V}O_2$max response to exercise were reported in the large-scale Dose-Response to Exercise in Women (DREW) Study (Sisson *et al*., 2009). A decrease in the prevalence of non-response with increased training volume was also observed. The authors reported a large amount of inter-individual variability (-33.2 to 76.0% change), citing baseline $\dot{V}O_2$max, age and training volume as predictors of non-response. The study comprised three intervention groups (4, 8 and 12 kcal/kg per week of exercise) alongside a control group, with a stated purpose of the analysis to examine the determinants of change in $\dot{V}O_2$max in response to exercise training. However, the decision to exclude the control group from the analysis compromised the correct quantification of the true inter-individual response and missed potentially vital information. Further work from the DREW study reported that 30% of participants experienced no improvement in $\dot{V}O_2$peak (Pandey *et al*., 2015). However, once again, no control group data were studied.

Recent studies have been undertaken to further identify possible genotype or phenotype interactions responsible for moderating the magnitude of inter-individual response (Hautala *et al*., 2003, Karavirta *et al*., 2011, Ross *et al*., 2015). Large

variation in training response to an eight-week aerobic endurance training intervention was reported (Hautala *et al*., 2003). Interestingly, whilst a control group was used, the baseline to follow-up changes in this group were not used for comparison at all. Disregarding the control group in this manner, on the basis that there will be no mean change, and/or the short-term test-retest reliability is high, is an approach that has limitations. Differences in response were observed by dividing the intervention group responses by quartile, rather than retaining a continuous variable; this approach discards information and has previously been reported to be an inadequate analysis method in epidemiology (Benette & Vickers, 2012). I found that, during my re-analysis of these data, in contrast to the authors' assertion of the differential effects of the sympathetic nervous system on the responses to the training protocol, it appears that there may be little true difference in the variation (SD_{change}) between each of the 'response' groups (SD_{change} range 1-2 $mL.kg^{-1}.min^{-1}$).

3.4.3 Concurrent Training

Investigations into the inter-individual responses to combined endurance and strength training in young (Hautala *et al*., 2006) and older adults (Karavirta *et al*., 2011) have also been undertaken. The findings of these studies are in general agreement with much of the previously published literature, in that a range of training responses were observed. Nevertheless, as in an earlier study (Prud'homme *et al*., 1984), a control group was included in one study (Karavirta *et al*., 2011) but no specific comparison was made. It is also apparent from the responses reported in Figure 1 of this investigation (Karavirta *et al*., 2011) that similar variation in response exists in the control group as in the experimental groups, reinforcing the view that there is similar variability of baseline to follow-up changes across all groups. The participants in another study acted as their own control in a crossover trial (Hautala *et al*., 2006), however, the residual training effect of the intervention period on the response following the washout period is unknown.

3.4.4 Biological Variability

Not all inter-individual response may be due to the factors postulated in the studies reviewed within this article. Neither does variation in responses confirm that this

assumption of inter-individual difference in response is true for any particular study (Atkinson & Batterham, 2015). Small day-to-day changes cannot be classified as a worthwhile change, and the response must be clinically relevant and more than the natural biological variation between baseline and follow-up measurements (Scharhag-Rosenberger *et al*., 2012). Of course, patients differ not only by genetics, but also by their personal history and environmental circumstances (Senn, 2001), and this can lead to a multitude of effects on inter-individual response. There appears to be little doubt that the response to exercise training is influenced by multiple factors.

A new focus on the quantification of true inter-individual differences and the moderators and mediators responsible may, therefore, have substantial clinical relevance, with any correctly quantified heterogeneity affording the opportunity to identify possible molecular determinants (Bouchard *et al*., 1999). Indeed, RNA profiling may be a potential methodology for capturing information critical to informing the integrated physiological response and molecular determinants (Timmons *et al*., 2010), once the presence of inter-individual variation in response has been confirmed.

3.4.5 Identifying 'Responders' and 'Non-Responders'

A further limitation of much of the previous research is the classification of individuals as 'non-responders' (Bouchard *et al*., 1999, Skinner *et al*., 2001) without first defining the term, although this has been partially addressed more recently when defined as those improving by 'less than the natural biological variability of the selected variable' (Scharhag-Rosenberger *et al*., 2012). Strictly, a positive response should be defined as an increase that is greater than the MCID. For $\dot{V}O_2$max, for example, the MCID could be defined as 1 MET, anchored to a clinically relevant relative risk reduction for all-cause mortality of around 12% for this value (Myers *et al*., 2002). For a given individual, the observed change in $\dot{V}O_2$max after the intervention can be combined with knowledge of the natural random variation of $\dot{V}O_2$max over the same time period (from a control group or similar reliability study) to derive the probability that this individual's true response is greater than the MCID (Hopkins, 2015). We can then more properly describe each individual in the

intervention as, for example, ‘likely to be a responder’, ‘very unlikely to be a responder’, ‘possibly negative responder’, and so on.

Similarly to previous reports (Sisson *et al*., 2009), further argument for the dose-response to exercise is observed when greater exercise volume (Pandey *et al*., 2015) or intensity (Ross *et al*., 2015) was associated with reduced chances of being classified as a non-responder. While direct comparison between studies is not straightforward, these and similar findings suggest that some people may be more sensitive to dose prescription of exercise, as opposed to being non-responsive. If this is the case, effective identification of dose requirement or requirement for multimodal approaches such as concurrent training may provide a capability for enhancing the efficacy of an intervention (Buford *et al*., 2013). However, as is covered in this review, I suggest that an individual cannot be categorically defined as a ‘responder’ or other such descriptor; merely a probability (percentage chance) that they are such can be applied to each individual (Hopkins, 2015). Even with this information, in a single-period before-and-after study design, this process can only occur in the presence of an appropriate comparator group assessed over the same or very similar time period as the exercise intervention.

3.4.6 The HERITAGE Family Study

The large-scale, longitudinal, multicentre HERITAGE Family Study was initiated to investigate and identify the role of genotype in cardiovascular, metabolic and hormonal responses to a 20-week aerobic exercise training programme (Bouchard *et al*., 1995). The contribution of regular exercise to changes in cardiovascular disease (CVD) and diabetes mellitus risk factors was also investigated (Bouchard *et al*., 1995, Gagnon *et al*., 1996). To date, 186 separate publications have resulted from the study, with some of these involving the comparison of various familial relationships to determine the relative importance of genetics (Bouchard *et al*., 2000, Perusse *et al*., 2000, Bouchard *et al*., 2011). The bulk of the research undertaken during HERITAGE asserts that there are no genotype-specific covariate effects on $\dot{V}O_2$max response, such as age, sex or weight (Bouchard & Rankinen, 2001, Skinner *et al*., 2001, Feitosa *et al*., 2002). Familial aggregation was reported in response to maximal (Lortie *et al*., 1984, Bouchard *et al*., 1998, Bouchard *et al*., 1999) and

submaximal (Gaskill *et al*., 2001, Perusse *et al*., 2001) aerobic training, with two and a half times more variance reported between than within families for the $\dot{V}O_2$max response.

A genetic contribution to this variance of approximately 47% has been reported (Bouchard *et al*., 1999, Bouchard *et al*., 2011). These data were characterized by a strong maternal aggregation (Bouchard *et al*., 1998, Bouchard *et al*., 1999, Perusse *et al*., 2001), with shared environmental factors also contributing to the observed heritabilities. The mechanisms underpinning this variance are unclear, but suggestions of genetic contribution from mitochondrial DNA (Bouchard *et al*., 1999) or expression of genes inherited from the mother have been presented (Perusse *et al*., 2001). Correlations between spouses have led to familial environmental factors also being postulated as responsible for some of the variance observed in response to exercise (Perusse *et al*., 2001, Bouchard *et al*., 1998, Montoye & Gayle, 1978, Lesage *et al*., 1985); however, the correlations presented are small (r=0.14-0.26), therefore posing, rather than answering, further questions on this issue. The crucial question that is, again, unanswered in the absence of a comparator group is whether there are genetic influences on individual magnitude of random within-subjects variability. If this is known, then these genetic influences could be quantified.

In HERITAGE studies, it is claimed that there is considerable variation in response. Nevertheless, it remains unclear as to whether it was the same individuals that showed no response for all measures, or if each individual showed differing response characteristics across the spectrum of physiological markers investigated. Recent research has attempted to elucidate this issue, observing improvements in at least one measured variable in every individual (Scharhag-Rosenberger *et al*., 2012), though again, this study is limited by the lack of a control group with which to compare the inter-individual response. Interestingly, despite methodological concerns, individuals with the highest response to endurance training have also shown high response to resistance training, but the reverse was not true (Hautala *et al*., 2006). This area opens up future avenues in which to investigate the magnitude of response, in the presence of proper initial quantification through comparison with a suitable comparator sample.

3.4.7 Twin Studies

Previously noted criticisms of twin studies point to the fact that they may not necessarily separate genetic from environmental pathways (Maes *et al*., 1997). Presentation of evidence of genetic variance of numerous phenotypes through greater between-twin pair variance than within-pair variance is often reported through the use of ICCs (Prud'homme *et al*., 1984, Hamel *et al*., 1985, Timmons *et al*., 2010, Poelhman *et al*., 1986, Bouchard *et al*., 1986, Heller *et al*., 1993, Bouchard *et al*., 1994, Hong *et al*., 1997, Tremblay *et al*., 1997) (Table 3). These observations are highly sample-specific, and a comparison of the ICC between studies is not without difficulty, due to the heterogeneity of samples. The potential for ICCs in twin studies to overestimate heritability has also been highlighted in that genetic and environmental factors have not been adequately separated (Heller *et al*., 1993).

It is as yet unknown as to whether any relationship between genes and phenotype is even linear (Maes *et al*., 1997) and while genetic variation is not denied in this review, it is not clear that all observed variance is genetic (Senn, 2001). I believe that when analysing such a design, it would be more appropriate to use data from a relevant control (no-exercise) sample and a linear mixed model in order to correctly quantify the influence of genetics on magnitude of response. Associations could then be presented as a regression coefficient in the units of measurement, rather than a comparison of correlation values. In this way, the clinical importance of any association can be inferred. Common underlying environmental effects have also been proposed as being underestimated due to study design or low statistical power (Segal & Allison, 2002). Adoption studies combined with twin studies to compare identical and fraternal twins and twins reared apart (Heller *et al*., 1993) and repeated assessments (Hecksteden *et al*., 2015) may be required to quantify some of these issues.

3.4.8 Baseline Correlation of Changes

Several authors of HERITAGE studies correlated each individual's baseline score with the follow-up change to attempt to determine the contribution of baseline status to the inter-individual response to exercise training. From such analyses, it has also

been reported that age, sex, fat mass, fat-free mass, weight and race have little or no impact upon the inter-individual response to training or covariate effect (Bouchard & Rankinen, 2001, Feitosa *et al*., 2002), and that the initial level of the phenotype was a major determinant of the magnitude of response in some cases (Bouchard & Rankinen, 2001). Nevertheless, this correlation approach has been questioned, due to regression to the mean and mathematical coupling influences (Chiolero *et al*., 2013). Linear mixed effects modelling and other methods such as computing regression to the mean slopes and then adjusting for the random error in initial measurement, as previously reported (Blomqvist & Svardsudd, 1978), have been purported to be superior to this simple correlation approach (Chiolero *et al*., 2013).

3.4.9 Testing Quality Control

The HERITAGE intervention was described as having a careful and constant program of quality control and quality assurance (Gagnon *et al*., 1996). Nevertheless, this claim was based on the test-retest mean differences being small, although the selection of either an average of two $\dot{V}O_2$max test scores (where coefficient of variation (CV) was less than 5% between the two) or the higher score (if CV was greater than 5% between the two) at both baseline and follow-up (Shephard *et al*., 2004) could have led to inconsistent data. To accurately analyse the data, identical methodology should ideally be used for all participants. Test-retest reliability was reported to be 4.1-5.0% and ICCs of 0.96 to 0.97 were reported over a period of two days (Shephard *et al*., 2004) and two weeks (Skinner *et al*., 1999), implying adequate short-term reproducibility. It is my belief that reproducibility needs to be assessed over a longer period, preferably matching the length of the intervention, in order to estimate the true extent of longer-term within-subject variation. A better alternative is to use an RCT design, wherein the control group in effect acts as the perfect contemporaneous reliability study. Each of the investigations discussed have contained a single application of an intervention (single period before-and-after study). It is reiterated that the primary limitation of the parallel group RCT design in permitting the quantification of inter-individual variation in treatment response is that it does not allow the isolation of the variance due to true subject-by-treatment interaction (Senn, 2016). In this design, the SD for inter-individual responses – although free from random error - includes the subject-

by-treatment interaction plus any within-subject variability in treatment response introduced by the intervention (Hecksteden *et al*., 2015). Indeed, the multiperiod (replicate) crossover study, in which participants are randomised to sequences in which they receive both the intervention and comparator treatments in at least two periods each, is the only design that can identify variance between-treatments, between-subjects, and the subject-by-treatment interaction (Hecksteden *et al*., 2015). However, the primary limitation of the replicate crossover, in the context of chronic training studies, is the long and uncertain washout periods required and hence potentially substantial carryover effects (Hopkins, 2015).

The authors of a recent investigation into the cardiac determinants of individual response in change in aerobic fitness after a moderate intensity exercise intervention (Pandey *et al*., 2015) stated that they incorporated 'well-controlled exercise trials' in keeping with the HERITAGE study. Nevertheless, 'well-controlled' appears to refer to relatively short-term repeatability of measurements (over a few days) rather than the within-subjects variability in measurements over the duration of the intervention (a few months). Just because a measurement method has good short-term repeatability does not rectify the problem of lack of a control group, which must be employed in order to make a formal comparison of the variability of the change scores in intervention vs. control groups.

Consequently, the inclusion of data from studies such as these is potentially misleading, and as such, participants from these studies that have been termed 'responders' and 'non-responders' may have been selected for further investigation as to the potential moderators and mediators of the inter-individual response, when it may be nothing other than their natural biological variation that has been measured.

3.4.10 *N*-of-1 Trials

In pharmacogenetics, *n*-of-1 trials have been proposed (Guyatt *et al*., 1990, Lillie *et al*., 2011), but these single-subject trial studies have previously been linked to controversial issues in clinical investigation, such as carryover effects and the presupposition of patient-by-treatment interaction, which requires random effects modelling (Senn, 1993), that may confound the effectiveness of interventions. Of

course, if a number of *n*-of-1 trials are carried out, then the combined data effectively equates to the repeated period crossover design proposed by Hecksteden *et al*. (2015). It has also been proposed that *n*-of-1 data with a limited observation count per participant may not be compatible with statistical models that aim to identify the inter-individual response and may be preferential for estimating the population effect (Zucker *et al*., 2010).

3.5 A Road Map for Future Study Designs and Analyses

Recently, for both parallel group and replicate crossover designs, more appropriate and robust statistical approaches have been forwarded for the quantification of true inter-individual response to a treatment. Relevant sources of variability must first be quantified (Hecksteden *et al*., 2015) before any exploration is undertaken of the true inter-individual variation in treatment response. Additionally, without knowledge of the smallest worthwhile change or the MCID, no substantial inter-individual differences in $\dot{V}O_2$max response to an exercise intervention can be claimed. When analysing the collected data from a parallel group RCT, it has been proposed that comparing the standard deviation of the intervention arm of the study against the standard deviation of the comparator arm, using $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$, where IR = inter-individual responses, I= the intervention sample SD and C = the comparator sample SD (Hopkins, 2015, Atkinson & Batterham, 2015), provides a more accurate statistical analysis of the presence of inter-individual differences in response. If appropriate clinical inferences are to be made about the magnitude of change and any inter-individual response to the intervention then standard deviations, confidence intervals, effect sizes and magnitude-based inferences should also be interpreted (Hopkins, 2015, Batterham & Hopkins, 2006). Using a custom spreadsheet (Hopkins, 2000), and with knowledge of the typical error over the same timeframe as the intervention and the smallest worthwhile change, the probability (percentage chance) of each individual being classified as ‘very likely’, ‘likely’, ‘possibly’, ‘possibly not’, ‘unlikely’ and ‘very unlikely’ to be a responder can be calculated.

This is a more robust approach, as the standard parallel arm study design renders the definitive identification of specific individuals as non-responders impossible (Leifer

et al., 2015) and, despite recent criticisms (Sainani, 2018), magnitude-based inferences are a valuable advance on hull hypothesis significance testing (Hopkins & Batterham, 2018). For instance, individuals could be termed likely 'positive' responders if the individual probabilities were above 0.75 (75% chance, or odds of 3:1 in favour) and the converse for 'negative' responders. A finding of substantial clinically relevant inter-individual differences in response to the intervention would justify further investigation of potential moderators and mediators, using more advanced statistical modelling.

If we consider the original pre-HERITAGE study (Prud'homme *et al*., 1984), the mean $\dot{V}O_2$max improvement in the exercise intervention group was 5.5 (± 3.7) $mL.kg^{-1}.min^{-1}$ and the change in the control group was -0.6 (± 5.6) $mL.kg^{-1}.min^{-1}$. The pooled between-subjects SD for $\dot{V}O_2$max at baseline was 5.9 $mL.kg^{-1}.min^{-1}$. If we define a 'responder' by an improvement of 1 MET, an individual would be required to improve by 7.4 $mL.kg^{-1}.min^{-1}$ (i.e. approximately 1.25 SDs) for the probability of being a true responder to be 0.75. To increase confidence, using a probability of 0.95 (i.e. 'very likely' to be a responder), the individual would be required to improve by 13.5 $mL.kg^{-1}.min^{-1}$, or more than 2 SDs. Therefore, an individual who showed an improvement of, say, 5 $mL.kg^{-1}.min^{-1}$ (a figure above the clinically relevant threshold for a responder of 1 MET) would have a probability of 0.60 of being a true responder. Obviously, in this case, this is little better than chance. These figures demonstrate that an individual would be required to improve their $\dot{V}O_2$max substantially more than the MCID (i.e. 1 MET) in order to be deemed likely or very likely to be a responder. This is in stark contrast to the practice of classification of any individual showing improvement of 3.5 $mL.kg^{-1}.min^{-1}$ (1 MET) or more as a definite responder. Assuming normal distribution of the changes in the control group and a MCID of 1 MET, the mean and SD reveal that 23% of the control group would be expected to 'improve' by more than 1 MET and would be labelled conventionally as 'positive responders'. These apparent positive responses in the control are due to the random variation in $\dot{V}O_2$max over a 20-week period. As highlighted, the SD of the change scores in each group reveal that there are no substantial inter-individual responses in the intervention group (vs. control), and any further investigation of the mechanisms underpinning inter-individual response from this study is therefore unwarranted.

In contrast to my proposed approach, it has been argued that a large-scale multiperiod crossover training study approach is a more robust method of predicting training response (Hecksteden *et al*., 2015). This approach, however, presents a number of challenges. Given the difficulties of recruiting the sample size required for a large-scale training study, this type of study is likely to be statistically underpowered, while the time required to run a training intervention study, complete with washout periods, is highly restrictive. The crossover trial methodology might also have less relevance in training studies than in pharmacological research, as the effectiveness of any washout period is unknown, and may diminish training related effects. This approach has been previously utilised through the use of a two-month washout period subsequent to a two-week intervention (Hautala *et al*., 2006), but the effects of the previous training intervention cannot be controlled for, and therefore each participant is potentially beginning from a different baseline. Unlike in pharmacological studies, where the washout period for specific drugs is defined as some multiple of the drug's half-life, it cannot be stated with any certainty that a previous period of training or an exercise intervention has not changed the individual at the cellular or neuromuscular level. This problem leads to a sample that is not acting as its own control, and therefore presents potential differences at baseline for each intervention period. The multiperiod crossover design might be more applicable to the investigation of acute effects of short-term interventions (Karavirta *et al*., 2011). There are also a multitude of sources of variability that create challenges in identifying true inter-individual differences in response in any research design, such as maturation, diet modulation, disease, lifestyle and environment to be accounted for, further confounding the issue (Buford *et al*., 2013).

3.6 Conclusions

To date, the investigation of inter-individual differences in $\dot{V}O_2$max response to exercise training has been conducted almost exclusively without a control group or comparator arm. While I do not deny that the identification of any inter-individual

Table 3. Twin studies presenting intraclass correlations in analysis of inter-individual response to exercise interventions. These ICCs may be inflated due to their inability to separate genetic and environmental influences

Literature Citation	Number of twin pairs	Mean (SD) age (years)	Outcome Measures	ICC	Age/Sex adjustment
Prud'homme *et al.*, 1984	10 MZ (6F, 4M)	20 (2.9)	MAP, VAT, VANT	0.74	Not reported
Bouchard *et al*., 1986	53 MZ (mixed sex) 33 DZ (mixed sex) 27 male siblings	16-34 (range)	$\dot{V}O_2$max	0.85 0.74 0.55	Yes
Hamel *et al*., 1986	6 MZ (3M, 3F)	21 (4)	$\dot{V}O_2$max	0.69	Not reported
Simonaeu *et al*., 1986	14 MZ (7M, 7F)	21.1 (3.3)	CK, FT proportion, enzymes	Not reported	Not reported
Poehlman *et al*., 1986	6 MZ males	19.2 (2.3)	Body comp, fat mass & morphology, skinfolds	0.46 – 0.90	Not reported
Bouchard *et al*., 1990	12 MZ males	21 (2)	Body comp & fat topography	0.4 – 0.55	Not reported
Heller *et al*., 1993	46 MZA, 67 MZT; 100 DZA, 89 DZT	52-86 (range)	Lipids	0.22 – 0.79, 0.33 – 0.83; -0.60 – 0.47, -0.13 – 0.49	Dichotomous age categories divided at median age
Hong *et al*., 1997	45 MZA, 64 MZT; 95 DZA, 85 DZT		Insulin, Glucose, Lipids, BP	0.5 MZ 0.15 DZ	Yes
Tremblay *et al*., 1997	11pr MZ males	21 (0.8)	RMR, fat loss, weight loss, FFM loss	0.32 – 0.69	Single sex, low SD of age

*Data table with ICC is not provided in the published paper. ** Study reports twins were self-report MZ or DZ. Age not mentioned

ICC intraclass correlation, MZ monozygotic, MAP maximal aerobic power, VAT ventilatory aerobic threshold, VANT ventilatory anaerobic threshold, DZ dizygotic, $\dot{V}O_2$max maximal oxygen uptake, CK creatine kinase, FT fibre type, MZA monozygotic twins reared apart, MZT monozygotic twins reared together, DZA dizygotic twins reared apart, DZT dizygotic twins reared together, FFM fat free mass, BP blood pressure, RMR resting metabolic rate

response to an exercise intervention is important, I maintain that the variation must be appropriately quantified prior to deeper investigation and recognize that a number of challenges exist in realising this goal. Primary among these is the proper quantification and determination of a threshold for meaningful magnitude of change, to establish the presence of clinically important differences in response (Buford *et al*., 2013). In order to quantify the inter-individual response to an exercise intervention, studies should contain the presence of a comparator arm, preferably as an RCT design. A number of variables and health outcomes should also be collected, as some participants may improve across some but not all physiological measures. However, these will come at greater research cost, and must be justified from an ethical standpoint. Furthermore, the correct statistical analysis and modelling must be used in order to identify the presence of true, clinically relevant, individual response, as unless true inter-individual response exists, it is futile looking for treatment interactions (Senn, 2004).

Future work on any primary outcome in exercise intervention trials should focus upon a thorough systematic review of the available literature, in order to determine the robustness of the published data addressing inter-individual differences in response to exercise training. Secondary analysis of the data presented by fellow researchers should also be undertaken, in order to quantify inter-individual responses in previous trials. Only when these effects have been properly quantified, using the standard deviation of the change score (SD_{change}) after adjusting for random within-subjects variability using the following equation: $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$ (18,19) can the design of experiments to further elucidate the mechanisms responsible for the individual response be confirmed. Supplementary investigations and robust data analysis must then be carried out, using a logical framework (Fig. 2) such as that previously proposed (Atkinson & Batterham, 2015) in order to properly identify whether specific moderators and mediators exist that control the likelihood of an individual responding to an exercise intervention, rather than looking to unravel complex gene responses. At this point, when included as covariates, these moderators and mediators may account for the inter-individual response, to the

extent that they reduce the magnitude of the SD for inter-individual responses (Karavirta *et al*., 2011).

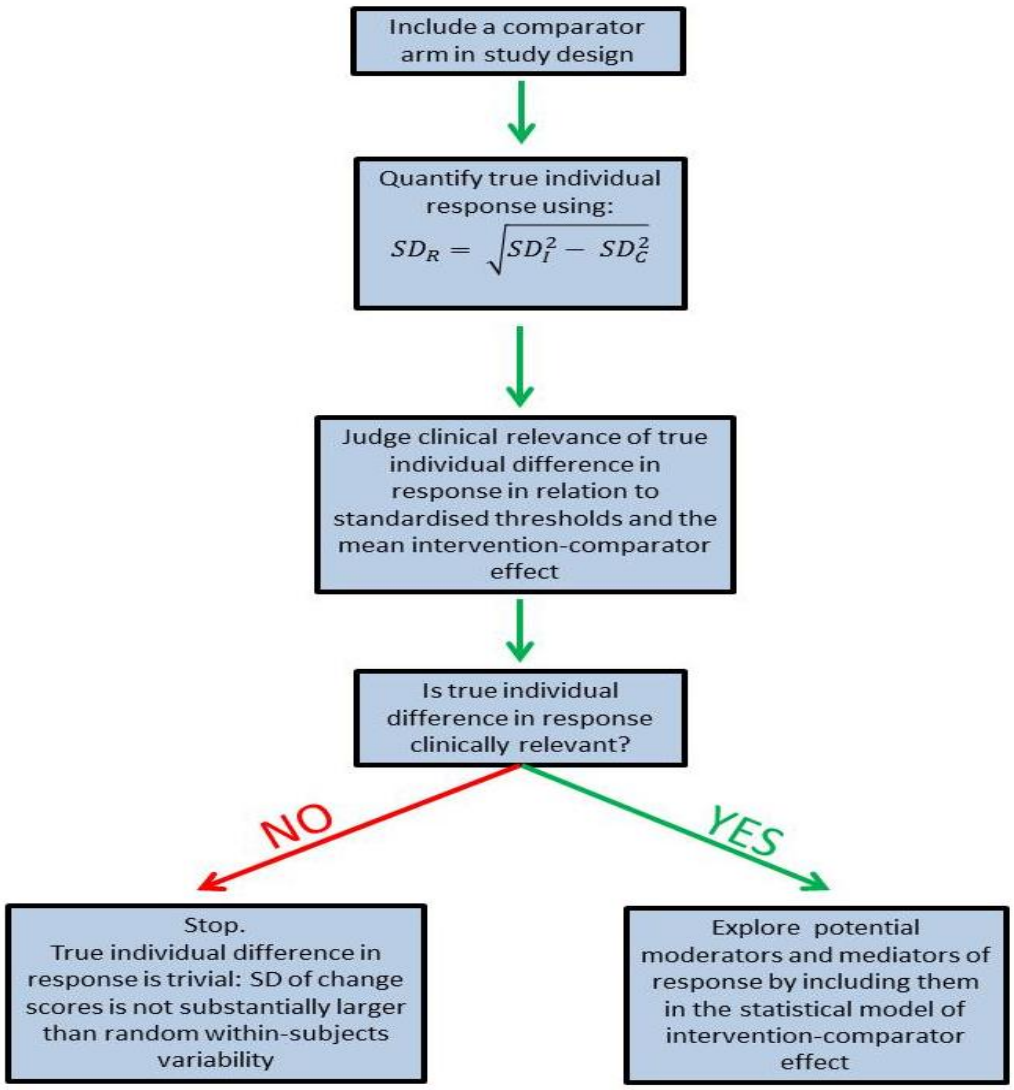

Fig. 2. Conceptual framework for the quantification of true inter-individual differences in response to an intervention.

In summary, against the backdrop of suggestions of precision interventions, individuals may respond to treatment in a variety of ways; the intervention might be beneficial, ineffective, or harmful for different people. The issue of inter-individual differences in the response of maximal oxygen uptake following an exercise intervention is very important and identifying the personal characteristics that account for these variations in response may ultimately allow more effective

direction of interventions. It is clear that the body of literature purporting to claim inter-individual variation in response does not, at this time, do so. Common themes in previous trial design and data analysis are evident, such as a lack of comparator arm or disregarding data from the control, and the use of ICCs to quantify genotype dependency of inter-individual difference in the variability of $\dot{V}O_2$max response. While the subject is an important one, it is crucial that the correct quantification methodology is employed, together with an understanding of the clinical importance of any inter-individual response, before suggestions can be made in regard to potential moderators and mediators responsible for the observed inter-individual variance of $\dot{V}O_2$max in response to exercise training.

Chapter 4: Inter-Individual Differences in Weight Change Following Exercise Interventions: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

4.1 Preface

The detailed review presented in Chapter 3 casts doubts upon the claims of inter-individual variation of maximal uptake in response to exercise training interventions. With this in mind, it is important to correctly quantify the inter-individual variation in response to exercise interventions. Whilst claims of individual variation have previously been made, this chapter presents a detailed systematic review and meta-analysis of studies aiming to elicit weight loss in response to an exercise intervention. Inter-individual variation in weight loss will be assessed in relation to a clinically-determined anchor, to determine whether any observed variation is clinically important.

Whilst this chapter discusses the findings from a weight loss meta-analysis, it is based upon a peer-reviewed research paper, published in *Obesity Reviews* in 2018 (Williamson *et al*., 2018).

4.2 Introduction

Interest in the individualised response to a treatment intervention, and its applicability to medical and exercise interventions, has been growing over the last three decades (Prud'homme *et al*., 1984, Lortie *et al*., 1984, Hamel *et al*., 1986, Rose & Parfitt, 2007, Senn *et al*., 2011, Bouchard, 2012, Bouchard *et al*., 2014, Mann *et al*., 2014) There has been specific interest in the inter-individual differences in weight change in response to exercise training for around 20 years (Snyder *et al*., 1997, Barbeau *et al*., 1999, King *et al*., 2008, Barwell *et al*., 2009, Cauldwell *et al*., 2009, Cauldwell *et al*., 2013). Such interest has developed into a dedicated field of research; precision medicine – encompassing 'tailor-made' therapies based on the individual response of a patient (Senn *et al*., 2011). It is predicted that this individual approach to medicine will ultimately reduce costs and improve quality of healthcare

(Spear *et al*., 2001). It has also been suggested that personalized medicine may revolutionize healthcare through utilization of individual genetic information, thereby improving drug safety and efficacy (Katsanis *et al*., 2008). Nevertheless, associations that have been reported between genotype and treatment responses are often small (Khoury & Galea, 2016).

A limitation of published research on the efficacy of exercise training has been reported to be the focus on group mean data, with inter-individual variation in response often being overlooked (King *et al*., 2008). Such a focus on mean effects could obfuscate important individual differences in response (Bouchard, 1983, Bouchard & Rankinen, 2001, King *et al*., 2008). If such individual differences are present, and predictors of individual response are identified, then targeted intervention strategies could be formulated to maximize weight loss for individuals.

A further limitation of much of the weight loss literature is the common use of expected weight loss calculations using the '3500kcal/lb rule', whereby an energy deficit of 3500kcal is predicted to induce a 1lb reduction in body weight, based on the calculation of body composition energy content (70:30 FM: FFM) (Wishnofsky, 1958). This approach has been criticized due to its erroneous predictions of linear changes in body weight (Melanson *et al*., 2013), while Hall *et al* (2011) identified that EE- induced rate of weight change slows over time. Therefore, predictions based on this '3500 kcal rule' may overestimate predicted weight loss. Likewise, models used to predict weight loss using energy balance based upon the first law of thermodynamics have been described as simplistic, inconsiderate to changes in in interactive components (Boutcher & Dunn, 2009) and changes in spontaneous physical activity (Donnelly & Smith, 2005). It is evident that there is a need to include body composition data and other markers of health, rather than just assessing the effectiveness of exercise based exclusively on body weight (King *et al*., 2009).

The lack of statistical power to detect changes is also an issue, as it is in many RCTs. Most trials only have sufficient power with which to detect overall main effects (Egbewahel, 2015), so subgroups such as those required to detect 'true' inter-individual response require even greater sample sizes to reduce the magnitude of the standard error and increase statistical power.

4.2.1 Research Design and Data Analysis Issues

There have been reports of inter-individual variation in adiposity and weight response to exercise (Snyder *et al*., 1997, Barbeau *et al*., 1999, King *et al*., 2008, Barwell *et al*., 2009), including observations that exercise can cause a less-than-expected weight loss for some individuals (Donnelly & Smith, 2005). It has been suggested that the response to exercise may be influenced by a multitude of individual characteristics, including sex (Ballor & Keesey, 1991, Donnelly & Smith, 2005), genetics (Simoneau *et al*., 1986), age, and baseline status of the measured outcome (Sisson *et al*., 2009). Inter-individual response variation should be quantified and judged properly (Atkinson & Batterham, 2015, Williamson *et al*., 2017) before the relevance of these effect modifiers of response are appraised, relative to a robust minimal clinically important difference (MCID). Crucially, this requires an appropriate control/ comparator group, preferably within a randomised trial design. Regrettably, substantial treatment response heterogeneity has been claimed from observations solely on the intervention group (King *et al*., 2008, Cauldwell *et al*., 2009, King *et al*., 2012). When the control sample is absent or ignored, the interpretation of response heterogeneity is prone to all the philosophical issues highlighted by Stephen Senn, particularly the problem of the "counterfactual" (Williamson *et al*., 2017).

An appropriate method to quantify "true" individual response variability in a parallel group study involves the application of the following equation; $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$ (Atkinson & Batterham, 2015, Hopkins, 2015), where SD_{IR} is the true inter-individual response variability, expressed as a standard deviation, and SD_I^2 and SD_C^2 are the standard deviations of the changes in the intervention and control samples, respectively. The SD_{IR} should be interpreted as the amount by which the net mean effect of the intervention (intervention minus control) differs typically between individuals (Hopkins, 2015).

4.2.2 Aims of the Review

In view of the above design and analysis issues, there is uncertainty about previously-drawn conclusions in weight-loss studies. To date, there has been no published quantitative synthesis of the evidence for individual response variation in studies on exercise-mediated weight loss. Therefore, I aimed to conduct a systematic review and meta-analysis of the available research to allow for quantification of 'true' inter-individual variation in weight change in response to an exercise intervention.

4.3 Methods

This study was undertaken in accordance with the ethics procedures and guidance of Teesside University. The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati *et al*., 2009). The review protocol was registered with PROSPERO, the International Prospective Register of Systematic Reviews (CRD42016049982). An initial scoping literature review was undertaken to gauge the likely number of eligible studies for inclusion in the meta-analysis, with the intention to identify whether there were sufficient studies to be able to conduct a robust meta-analysis.

4.3.1 Study Question

This systematic review was designed to address the following question:
Across all the relevant studies that include a suitable comparator sample, are there substantial (i.e. greater than a clinically-anchored MCID) inter-individual differences in body mass loss in response to an exercise intervention?

4.3.2 Literature Search and Study Selection

This review involved a systematic electronic search of peer-reviewed original literature using the following commonly used databases: Centre for Reviews and Dissemination (York), CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Cochrane Methodology

Register, Database of Abstract Reviews or Effects (DARE), Database of Promoting Health Effectiveness Reviews (DoPHER), EMBASE, Medline (Ovid), NHS Economic Evaluation Database (NHS EED), PROSPERO, PubMed, SCOPUS and Sport Discus. These databases were first searched in December 2016, before a secondary search in March 2017. The search strategy was designed to include all articles published in the English language. Search terms comprised of "exerc*" AND ("train*" OR "condition*") AND ("structure" OR "supervised") AND ("weight" OR "body compos**" OR "BMI*") AND ("randomi*" OR "RCT"). Subsequently, additional searches of reference lists, Google Scholar and relevant bibliographic hand searches with no limit of language or publication date were also completed. Only studies conducted in humans were considered.

Studies were screened for those that would meet the inclusion criteria. Titles and abstracts were initially scrutinised to exclude those studies clearly beyond the scope of this review. For potential studies that appeared to meet the inclusion criteria, or those for which a decision was unable to be made based upon the title and abstract alone, full, published articles were obtained for detailed assessment against the inclusion criteria. Where multiple papers from a single study have been published, these were treated as a single study. Included studies were randomized intervention studies, reporting the standard deviation of the change in body mass in both arms. All studies targeting specific populations (e.g. pregnant women, children, and individuals suffering from specific diseases) were excluded. The remaining full-text articles were included in the systematic review and meta-analysis. A complete overview of the process is presented at Fig. 3 and a comprehensive summary of the studies reviewed is presented in Table 4.

Two reviewers (myself and Greg Atkinson, PhD supervisor) independently assessed publications for eligibility. The decision to include studies was hierarchical and made initially upon the basis of the study title, abstract and presence of keywords. When a study could not be excluded with certainty, the full text was obtained for evaluation. Disagreements between reviewers were resolved through discussion with a third reviewer (Alan Batterham, PhD Director of Studies) and a consensus approach was used.

4.3.3 Study Eligibility

4.3.3.1 Inclusion Criteria

To be included for quantitative synthesis, studies were required to meet the following criteria: (1) participants were required to be aged 18 or over; (2) taking part in studies where the experimental arm was an exercise-based intervention; (3)

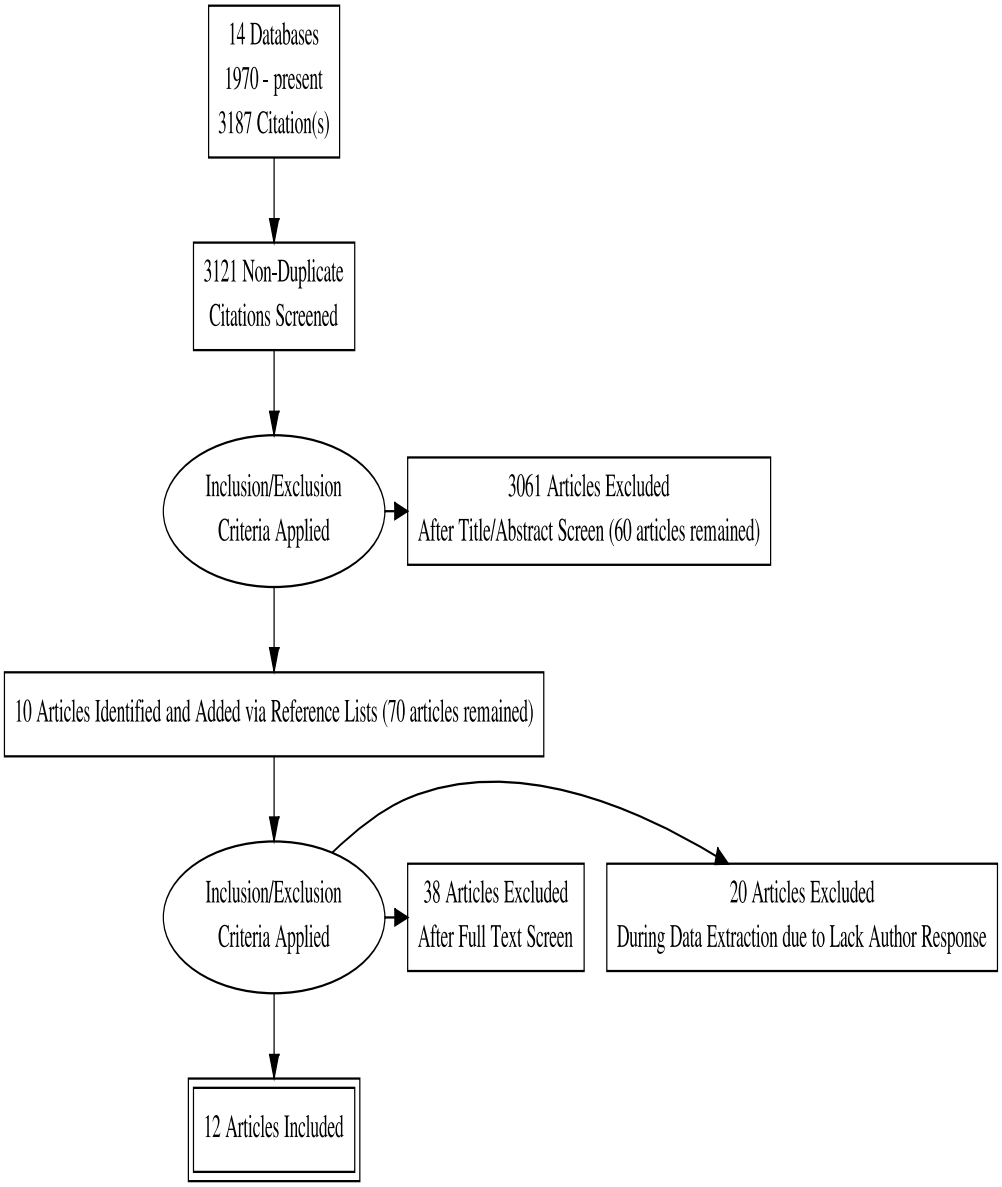

Fig. 3. PRISMA flowchart detailing stages of search

which was designed to elicit weight loss; (4) reporting change in adiposity indices (body mass index, body fat or body weight); (5) with no history of diabetes, metabolic, cardiovascular, musculoskeletal or inflammatory disease; (6) the exercise intervention was required to be supervised; (7) the investigation had to be an RCT design; and (8) greater than six weeks in duration. Since the interventions were exercised-based, participants were not blinded. Studies were included if they were published in peer-reviewed journals or full manuscripts were available (i.e. theses and dissertations). Where several intervention arms were present, all data other than that from the control-only and exercise-only arms were excluded. Where more than one exercise intervention was present, results were combined to avoid double counting of the control sample (Ryan, 2013). The same procedure for combining groups was applied to studies with a single exercise intervention but with results reported separately for sub-groups.

4.3.3.2 Exclusion Criteria

Studies were excluded if they (1) included unsupervised exercise interventions, behaviour therapy, dietary modification, health education, surgical, drug or hormone treatment that did not include exercise; (2) if change in body mass/ composition was not a primary or secondary aim of the study; (3) if no relevant comparator sample were present; or (4) the full-text manuscript was written in a language other than English.

4.3.4 Data Extraction and Synthesis

DigitizeIt (Brunschweig, Germany) graph digitizer software was used to extract precise data in cases where data were only presented in Figures rather than text.

Study characteristics such as study design, participant characteristics (age, sex, ethnicity), measurement methods, change scores, SD_{change} and information to assess the risk of bias were extracted by myself (see 4.3.5 Assessment of Study Quality).

A standardized data extraction sheet was used to collect data on participants' characteristics, study methods, sample size, prescribed intervention (frequency,

intensity, duration and type), outcomes assessed, loss to follow up and study type. The data for Table 4 was collected by myself before Professor Greg Atkinson verified its accuracy and the eligibility of studies for inclusion. Where data were incompletely or unclearly reported, the lead author contacted study authors for clarification. Effect sizes were calculated for the relevant measures.

4.3.5 Assessment of Study Quality

Methodological risk of bias was assessed and reported in accordance with the Cochrane Handbook (Higgins & Green, 2011) and the guidelines of the Cochrane Consumers and Communication Review Group (Ryan, 2013), which recommend the explicit reporting of the following elements for RCTs: random sequence generation; allocation sequence concealment; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data; selective reporting; and other sources of bias. Each item was judged as being at high, low or unclear risk of bias as set out in the criteria provided (Higgins & Green, 2011). A summary of risk of bias is presented in Figs 4 and 5, produced using RevMan software (Review Manager. Version 5.3. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2014).

Studies were deemed to be at highest risk of bias if they scored as high or unclear risk of bias for either the sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins & Green, 2011).

In all cases, risk of bias was independently assessed, with any disagreements resolved by discussion to reach consensus. Risk of bias results were incorporated into the review using standard tables and commentary about each element, leading to an overall assessment of the risk of bias of those studies selected for inclusion and a judgement about the internal validity of results.

4.3.6 Meta-Analysis

First, to put the results for individual response variance in context I conducted a

random-effects meta-analysis for the mean difference in weight loss across the included studies, using a restricted maximum likelihood (REML) model combined with the Knapp-Hartung method (t-distribution for between-study variance). Second, for each study I extracted the standard deviation of the changes in body mass for both control (C) and exercise intervention (I) groups. The true individual response variance (intervention minus control) was then derived as $SD_I^2 - SD_C^2$. The standard error (SE) for this variance was calculated using the following equation: $SE = \sqrt{[2(SD_{Exp}^4/DF_{Exp} + SD_{Con}^4/DF_{Con})]}$, where DF_{Exp} and DF_{Con} are the degrees of freedom of the standard deviations in the exercise and control groups (Liberati *et al*., 2009). Note that a negative value for the individual response variance, for either the point estimate or lower bound of the confidence interval or prediction interval, implies greater variability in the changes in body mass in the control versus intervention groups.

The individual response variances with their SEs were meta-analysed using a REML model combined with the Knapp-Hartung method. It is important to note that the variances are unbiased, whereas the SD is not, and deriving a SE for the SD for individual responses is also problematic. Therefore, synthesising the individual response variances rather than the SDs for individual responses is imperative. I derived the point estimate for the pooled individual response variance together with its uncertainty expressed as a 95% Confidence Interval (CI). The point estimate and confidence limits were then converted to an SD metric by taking the square root. In the case that the lower limit of the interval was negative, I first ignored the sign, took the square root, and then re-applied the sign. This approach is consistent with the 'nobound' option in SAS/STAT® software, which permits negative variances (SAS Institute Inc. 2017. *SAS/STAT 14.3 User's Guide*. Cary, NC: SAS Institute Inc.).

For both mean and inter-individual variation meta-analyses, between-study heterogeneity was quantified through the tau statistic (τ) – a SD describing the typical variability in the mean effect between studies (Higgins, 2008). Using the SE for the pooled mean effect and the tau, a 95% prediction interval was derived to quantify the expected range of true effects in future studies in similar settings (Inthout *et al*., 2016). For the individual response variability, this prediction interval was derived for $2 \times SD_{IR}$, as the SD_{IR} should be doubled before evaluating its

magnitude to reflect a comparison between a typically high (mean + SD_{IR}) and typically low (mean – SD_{IR}) responder (Hopkins, 2015). The magnitude of both the mean weight loss and the individual response variability ($2\times SD_{IR}$) was evaluated against a minimum clinically important difference for weight loss of 2.5 kg (Jensen *et al*., 2014) by calculating the probability that the effect in a future study in similar settings would exceed this threshold (Inthout *et al*., 2016). This probability was interpreted using the qualitative probabilistic anchors advanced by Hopkins *et al*. (Hopkins *et al*., 2009). Inasmuch as we must work with the response variances, rather than the SDs, I first halved the minimal clinically important difference (equivalent to doubling the SD for individual responses), squared it (to express it in variance metric) and then derived the probability that the response variance in a new study would be clinically relevant, as described above. The threshold of 2.5 kg for the MCID was chosen, conservatively, as the lowest value from the range of clinically relevant effects presented by Jensen *et al*. By definition, effects smaller than this threshold are defined as trivial (not clinically relevant). Effects >2.5 kg but <7.5 kg are defined as 'small' (yet clinically important). 'Moderate' effects are defined as >7.5 kg but <15 kg, and 'large' effects as >15 kg (Hopkins *et al*., 2009).

All statistical analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat Inc., Englewood, NJ, USA).

4.4 Results

4.4.1 Study Selection

The initial search generated 3187 results (Fig. 3). 3061 of these were excluded based on titles and abstracts alone, and 66 duplicates were rejected. The complete text was obtained for 60 articles. A further 10 were identified from relevant reference lists and hand searches. Following examination of these articles, 12 were identified that met the eligibility criteria and are summarized in Table 4. A further 20 met all selection criteria, apart from the reporting of SD_{change}. The authors of these papers were contacted, but only four responses were received, and full data were not provided in these instances (Schuit *et al*., 1998, Maiorana *et al*., 2001, Donnelly *et al*., 2003, Potteiger *et al*., 2003, Schmitz *et al*., 2003, Takeshima *et al*., 2004, Toraman *et al*.,

2004, Shojaee-Moradie *et al*., 2007, McTiernan *et al*., 2007, Nalbant *et al*., 2009, Coker *et al*., 2009, Kerksick *et al*., 2010, Atashak *et al*., 2011, Sheikholeslami Vatani *et al*., 2011, Donges *et al*., 2012, Tracy & Hart, 2013, Herring *et al*., 2014, Kim *et al*., 2015, Bittari *et al*., 2016, Tan *et al*., 2016). Contact was made by email. If, after four weeks, no response was received, a further email was sent. Following a further four-week period, papers from these authors were excluded. One paper met all inclusion criteria (Atlantis *et al*., 2006), except for the fact that median and interquartile range values were presented for changes in body mass, rather than means and SDs. No non-published studies (i.e., dissertations) were found to be eligible for inclusion.

The included studies encompassed a 17-year publication period between 1999 and 2016. Included studies involved a total of 1500 participants (EX: *n*=922, CON: *n*=578). Three trials involved outcomes of aerobic training interventions (Church *et al*., 2009, Tan *et al*., 2012, Donnelly *et al*., 2013), three involved the outcomes of resistance training interventions (Prabhakaran *et al*., 1999, Schmitz *et al*., 2002, Teixeira *et al*., 2003), one study involved the outcomes on separate aerobic and resistance training interventions (Donges *et al*., 2010) and five studies involved the outcomes of combined/concurrent training (Lockwood *et al*., 2008, Burtscher *et al*., 2009, Vilela *et al*., 2015, Baillot *et al*., 2016, Dalager *et al*., 2016). The duration of studies ranged from 8 to 52 weeks, study sample sizes ranged from 24 to 411 and reported pre-intervention mean body mass ranged from 65.5 to 128.0 kg.

4.4.2 Study Outcomes

The pooled mean group difference in pre/post changes in weight (intervention minus control) was -1.4 kg (95% CI -0.3 to -2.5 kg). Substantial between study heterogeneity was observed (τ=1.5 kg: -0.4 to 2.2 kg). The prediction interval revealed that, were investigators to undertake a future trial, the 95% plausible range for mean weight change vs. control would be -5.0 to 2.1 kg. The probability (% chances) that the mean weight loss (intervention minus control) in a future study in similar settings would exceed the minimum clinically important difference of a reduction of 2.5 kg was 26% ('possibly' clinically important).

The pooled point estimate for the inter-individual variability in weight change in response to an exercise intervention (SD_{IR}) was 0.8 (-0.9 to 1.4) kg. The between-study heterogeneity (τ) was 1.0 (-1.7 to 2.2) kg. The 95% prediction interval for 2 × SD for true inter-individual responses was -2.8 to 3.6 kg. The probability (% chances) that the individual response variability (2 × SD) in a future study in similar settings would be clinically meaningful (>2.5 kg) is 23% - 'unlikely' to be clinically important**.** Therefore, the odds are greater than 3:1 against the notion that there is clinically relevant individual response variance.

4.4.3 Study Quality and Risk of Bias

Table 5 and Figs 4 and 5 present a summary of risk of bias within included studies. Overall, risk of bias was mostly low or of unclear risk in the outcome of interest.

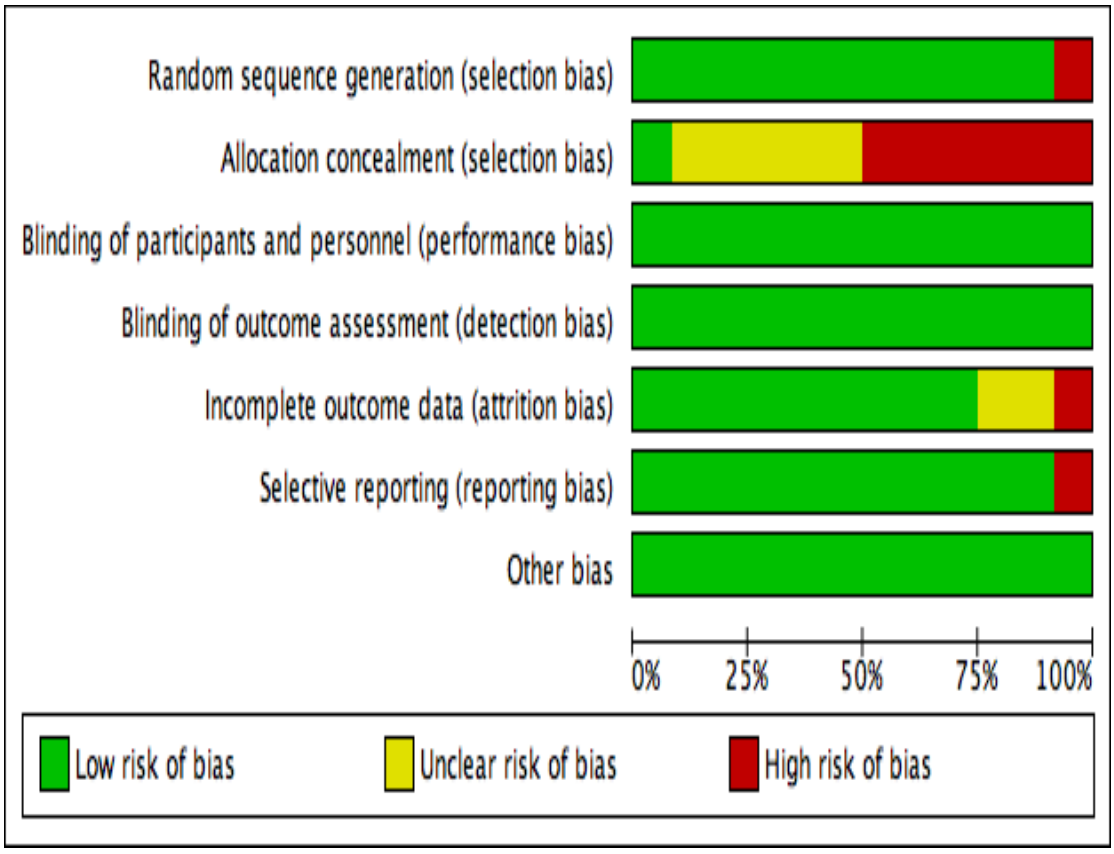

Fig. 4. Graph (visual summary of Table 4) detailing breakdown of risk of study bias, stratified by risk category. (Risk of bias determined using Cochrane guidelines)

Table 4. Studies presenting weight loss response to supervised exercise interventions.

		Exercise training program			Results	
Literature Citation	**Subjects/Groups**	**Mode**	**Length**	**Intensity/Frequency/Duration/Volume**	**Δ BW (kg) ± SD**	**Other**
Aerobic Training Interventions						
Church *et al*., 2009	*n* = 317 (EX), *n* = 94 (CON)	Aerobic training alternating treadmill and cycle ergometer	26 wk	3-4/wk, CON + 3 EX groups – 4, 8, 12 Kcal/kg BW, 50% $\dot{V}O_2$ alternating between semi-recumbent cycling and treadmills.	EX - 4 Kcal -1.4 (3.6), 8Kcal -2.1 (3.5), 12 Kcal -1.5 (3.4) Combined -1.62 (3.5), CON -0.9 (3.37)	No difference between predicted and actual weight loss at 4 & 8 Kcal/kg, 12 Kcal/kg lost only half predicted amount
Donnelly *et al*., 2013	*n* = 74 (EX), *n* = 18 (CON)	Aerobic training	10 months	5/wk, aerobic exercise – walking/jogging on treadmill (20% of sessions were undertaken on alternative activities such as stationary cycling, elliptical or walking/jogging outside), expending 400 & 600 Kcal/session	400 Kcal -3.9 (4.9), 600 Kcal -5.2 (5.6), Combined EX -4.55 (5.27), CON 0.5 (3.5)	No significant difference between exercise intervention, suggested some compensatory mechanisms, or when stratified by gender
Tan *et al*., 2012	*n* = 29 (EX), *n* = 19 (CON)	Track running	8 wk	5/wk, 40 mins of running at individualized Fat_{max} HR on outdoor track	EX -4.1 (1.6), CON 0.3 (1.2)	Fat_{max} also decreased fat mass, waist-hip ratio (both possibly related to change in fat oxidation rates), fasting plasma concentration (increased use of fat as fuel) and increased $\dot{V}O_2max$
Resistance Training Interventions						

Prabhakaran *et al.*, 1999	*n* = 12 (EX), *n* = 12 (CON)	Resistance Training	14 wk	3/wk, 45-50 mins/session, 85% 1RM, loading major muscle groups, 2 sets of 8 reps, 1 set to failure, 30-60 seconds rest	EX -0.7 (1.35), CON 0.49 (2.01)	Reduction in lipids and body fat % in EX
Schmitz *et al*., 2002	*n* = 27 (EX), *n* = 27 (CON)	Resistance training	15 wk	2/wk, 50 mins, 3 sets of 8-10 reps, 9 exercises	EX 0.54 (1.87), CON 0.49 (1.82)	Strength training produced favourable Δ in fasting glucose, insulin and cancer risk factors
Teixeira *et al*., 2003	*n* = 117 (EX), *n* = 116 (CON)	RT, circuit and weight bearing aerobic exercise	12 months	3/wk, RT 6-70 mins, 2 sets of 6-8 reps at 70-80% 1RM, AT included walking, jogging, skipping, hopping, 10 mins as WU, then 20-25 mins @ 60% HR_{max}	EX (with HRT/without HRT) -0.2 (2.6)/0.34 (2.5) combined SD 2.55, CON (with HRT/without HRT) 0.8 (2.7)/-0.4 (3.3), combined SD 3.05. Total EX 0.07 (2.55), CON 0.23 (3.05)	Δ LST in all who exercised and non-exercisers not taking HRT, decreased FT on women on HRT. HRT appeared to protect against loss of LST
Separate Aerobic and Resistance Training Interventions						
Donges *et al*., 2010	*n* = 76 (EX), *n* = 26 (CON)	Aerobic and resistance training	10 wk	RT 30-50 mins, 2-4 sets of 8-10 reps @ 70-75% of 10RM, AT 30-50 mins cycle ergometer 70-75% MHR	RT 0.8 (1.5), AT -0.8 (1.9), Combined – -0.06 (1.89) CON 0.6 (1.3)	AT > Δ in body composition than RT & CON. CRP reduced in RT, IL6 unchanged in all
Combined/Concurrent Training						
Baillot *et al*., 2016	*n* = 15 (EX), *n* = 14 (CON)	Endurance and circuit style with 9 stations	12 wk	3/wk, 80 mins - 10WU, 50-60MB (30mins endurance, including treadmill, elliptical, arm ergo cycle, 20-30mins strength), 10CD. Endurance at 55-85% HRR	EX -0.92 (3.55), CON -0.3 (4.72)	Pre-Surgical Exercise Training (PreSET) intervention also improved social interaction/ PA barriers

Burtscher *et al*., 2009	*n* = 18 (EX), *n* = 18 (CON)	Aerobic training, circuit training	12 months	2/wk, 60mins, aerobic exercise (dancing, walking, running, skating, swimming) eliciting lactate response of 2-3mmol/L, interspersed with higher intensity efforts. Circuits included 6-8 exercises, 8-12 reps. All participants also advised to exercise for 30mins/day	EX -2.58 (4.12), CON 0.79 (4.93)	Counselling & supervised exercise maintained exercise capacity vs counselling alone. In EX, dietary goals (<BW by 5%) not achieved
Dalager *et al*., 2016	*n* = 89 (EX), *n* = 195 (CON)	Aerobic and resistance training	1 yr	1/wk, 20 mins aerobic exercise (running, rowing, ball games) 77-95% HR_{max}, 30 mins resistance training 60-80% 1RM for three sets of 8 reps, recommendations to undertake 30mins exercise/day at 64-76% HR_{max}	EX -0.49 (3.32), CON 0.08 (2.97)	5% (ITT) and 10% (PPA) > Δ $\dot{V}O_2$max in EX than INT, 2.8% ∇in SBP
Lockwood *et al*., 2008	*n* = 14 (EX), *n* = 10 (CON)	Aerobic and resistance training	10 weeks	AT 3/wk, self-selected exercise 15-35 mins @ 40-70% HRR, RT 2/wk, 1 set of 8-12 reps (or to failure)	EX -0.3 (1.87), CON -0.3 (1.58)	Individual variation in *ad libitum* EI, linked with compensatory EI in EX
Vilela *et al*., 2015	*n* = 30 (EX), *n* = 30 (CON)	RT, sporting activity	4 months	5/wk, RT including 2 days upper body exercises and 2 days lower body exercises. 4 x 10mins 3 sets of 30secs work, 30secs recovery, 5 mins flexibility, 1 x 15 mins sporting activity	EX 0.0 (2.6), CON 0.4 (2.6)	EX reduced body fat by 4.8 (1.8) %, in the absence of weight loss, suggesting increased lean tissue

BW body weight, kg kilograms, SD standard deviation, EX exercise condition, CON control condition, wk weeks, mins minutes, WU warm-up, MB main body of exercise session, CD cool-down, HRR heart rate reserve, PA physical activity, Reps repetitions, mmol/L millimole per litre, Kcal Kilocalorie, $\dot{V}O_2$ oxygen uptake, Yr year, HR_{max} maximal heart rate, ITT intention to treat, PPA per protocol analysis, $\dot{V}O_2$max maximal oxygen uptake, SBP systolic blood pressure, RT resistance training, RM repetition maximum, AT aerobic training, CRP C-reactive protein, IL6 – interleukin 6, EI energy intake, Fat_{max} intensity of maximal fat oxidation, $\dot{V}O_2$max maximal oxygen uptake, HRT hormone replacement therapy, LST lean soft tissue, FT fat tissue, secs seconds.

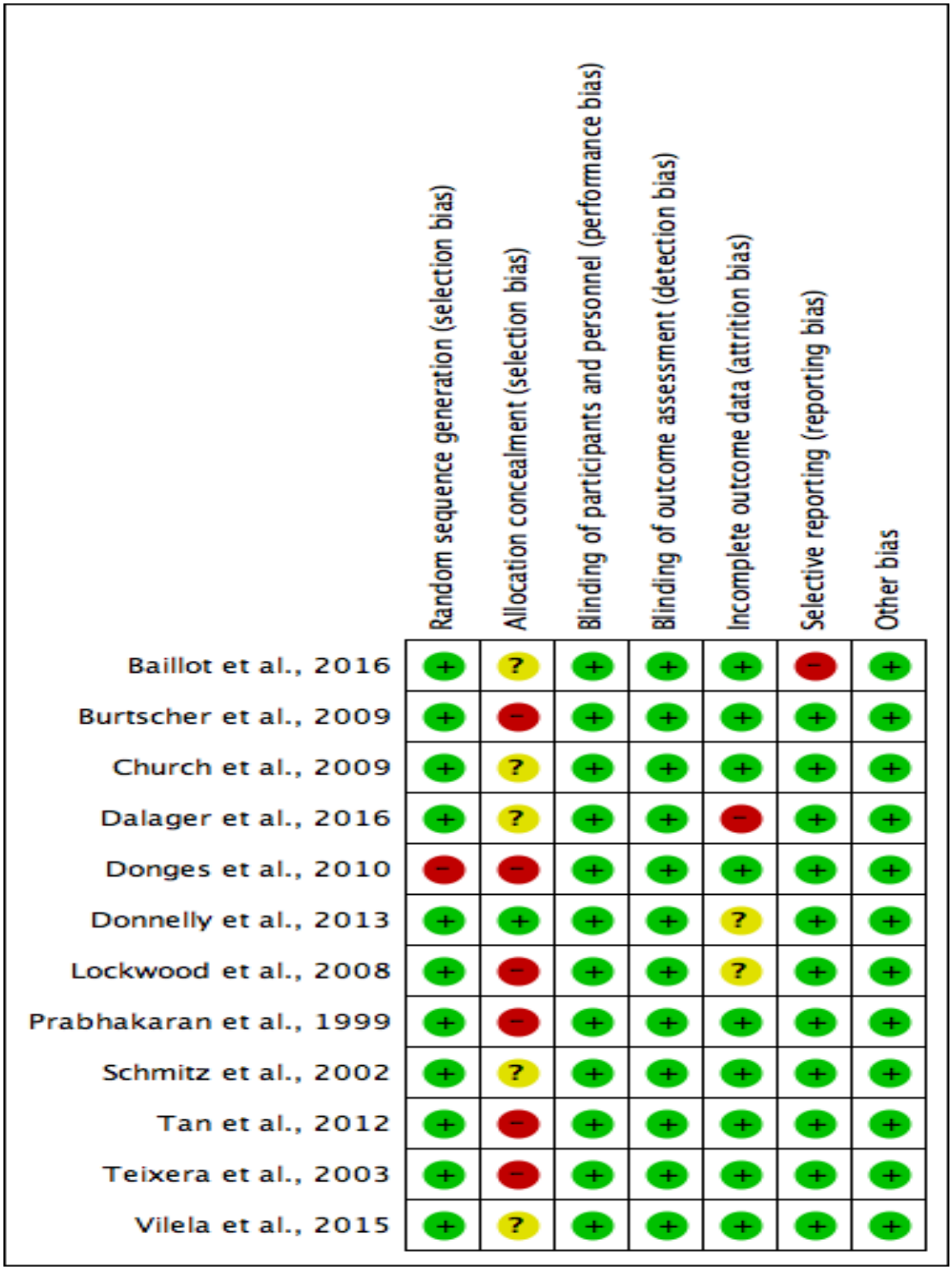

Fig. 5. Graph detailing breakdown of risk of study bias, stratified by study and specific risk factor

Table 5. Summary descriptives of risk of bias for each of the included studies, in accordance with Cochrane guidelines.

Literature Citation	Random Sequence Generation		Allocation Concealment		Blinding of Participants		Blinding of Outcome Assessment		Incomplete Outcome Data Addressed		Selective Reporting		Other	
	Risk	**Comment**	**Risk**	**Comment**	**Risk**	**Comment**	**Risk**	**Comment**	**Risk**	**Comment**	**Risk**	**Comment**	**Risk**	**Comment**
Baillot *et al*., 2016	Low	Quote "Patients were randomly allocated" Comment: Likely done	Unclear	Quote "Allocation was generated by a computer random sequence and kept in sealed envelopes" Comment: Likely done	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes	Low	Quote: "the only subject who abandoned the research project was in the usual care group and excluded from analyses". Comment: Likely done	High	Six domains for WRQL in methods, only one reported in written format; others presented in table format.	Low	The study appears free from other sources of bias.
Burtscher *et al*., 2009	Low	Quote "Patients were randomly assigned" Comment: Likely done	High	Comment: No information provided on method of randomization. Comment: Possibly not done	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes	Low	Quote: "Due to financial problems, we had to terminate the exercise program at Month 12. To minimize possible bias, 18 patients were then compared to age- and	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way.	Low	The study appears free from other sources of bias.

										gender-matched patients in a nested cohort approach". Comment: Likely done				
Church *et al*., 2009	Low	Quote "Patients were randomized to 1 of 3 exercise groups or a non-exercise control" Comment: Likely done	Unclear	Quote "The randomization sequence is computer generated by the study statistician" Comment: Statement found in published rationale paper. Possibly done	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes	Low	Comment: Missing data relatively balanced across intervention groups. Additionally, missing data were imputed by carrying forward from previous observation (1 week)	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way.	Low	The study appears free from other sources of bias.
Dalager *et al*., 2016	Low	Quote "Office workers were randomized 1:1 to a training group or a control group"	Unclear	Quote: "The participants were assigned with an arbitrary ID number and randomized individually,	Low	Comment: Exercise interventions preclude the blinding of participants to allocated	Low	Quote: "The study was a 2-year, parallel group, examiner blinded RCT".	High	Quote: "Missing values in either baseline or follow-up measurement	Low	Comment: Study protocol available and all pre-specified	Low	The study appears free from other sources of bias.

		Comment: Likely done		using a random number computer algorithm". Comment: Possibly done		group during the study. It is judged that this would not influence outcomes		Comment: Likely done		were substituted with data carried forwards or backwards". Comment: Missing data unbalanced across intervention groups. It is unknown as to what impact this might have on effect sizes.		outcomes reported in pre-specified way.		
Donges *et al*., 2010	High	Quote "Participants were semi randomly assigned….80% were randomly assigned, however 20% were allocated according to matching or preference".	High	Comment: No information provided on method of randomization, other describing it as 'semi-random'	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes	Low	Comment: No missing data apparent.	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way.	Low	The study appears free from other sources of bias.

Donnelly *et al*., 2013	Low	Quote: "Participants were randomized (2:2:1) to exercise or non-exercise". Comment: Likely done.	Low	Quote: "Participants were stratified by gender and randomized by an independent statistician". Comment: Possibly done.	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes	Low	Quote: "Investigators and research assistants were blinded at the level of outcome assessments". Comment: Likely done.	Unclear	Comment: No methodology for approaching massing data. Missing data relatively balanced across intervention groups.	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way.	Low	The study appears free from other sources of bias.
Lockwood *et al*., 2008	Low	Quote: "Subjects were randomly assigned" Comment: Likely done.	High	Comment: No information provided on method of concealment.	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes	Unclear	Comment: No methodology for approaching missing data. Missing data relatively balanced across intervention groups.	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way.	Low	The study appears free from other sources of bias.
Prabhakaran *et al.*, 1999	Low	Quote: "Subjects were randomly assigned to	High	Comment: No information provided on method of concealment.	Low	Comment: Exercise interventions preclude the blinding of	Low	Comment: No mention of blinding of outcome assessment. It	Low	Comment: Missing data relatively balanced across	Low	Comment: Study protocol available and all	Low	The study appears free from other

		either a non-exercising control group or a resistance exercise training group". Comment: Likely done.				participants to allocated group during the study. It is judged that this would not influence outcomes		is judged that this would not influence outcomes		intervention groups.		pre-specified outcomes reported in pre-specified way.		sources of bias.
Schmitz *et al*., 2002	Low	Quote: "Randomized to no-contact control or treatment". Comment: Likely done.	Unclear	Comment: Randomization stratified by decade (30-39, 40-50) due to concerns regarding effects of hormonal changes.	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes	Low	Quote: "Body weight and height measurements, blood draws and DEXA (body composition) were performed by clinical research nurses, blinded to treatment groups". Comment: Likely done.	Low	Comment: Missing data relatively balanced across intervention groups.	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way.	Low	The study appears free from other sources of bias.
Tan *et al*., 2012	Low	Quote: "Participants were randomly	High	Comment: No information provided on	Low	Comment: Exercise interventions preclude the	Low	Comment: No mention of blinding of outcome	Low	Comment: Missing data relatively balanced	Low	Comment: Study protocol available	Low	The study appears free from other

		allocated into two groups". Comment: Likely done.		method of randomization.		blinding of participants to allocated group during the study. It is judged that this would not influence outcomes		assessment. It is judged that this would not influence outcomes		across intervention groups. Additionally, reasons unlikely to affect outcome measures.		and all pre-specified outcomes reported in pre-specified way.		sources of bias.
Teixeira *et al*., 2003	Low	Quote: "Subjects were randomly allocated to assigned to one year of weight-lifting and weight-bearing exercise or to a group with no exercise." Comment: Likely done.	High	Comment: Subjects stratified by HRT status.	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes	Low	Quote: "DEXA technicians were blind to participants group assignments". Comment: Likely done.	Low	Comment: No missing data apparent.	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way.	Low	The study appears free from other sources of bias.
Vilela *et al*., 2015	Low	Quote: "Randomly distributed in control and experimental groups". Comment: Likely done.	Unclear	Quote: "Randomly assigned drawing an opaque envelope", with "names written on them".	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes	Low	Comment: No missing data apparent.	Low	Comment: Study protocol available and all pre-specified outcomes reported	Low	The study appears free from other sources of bias.

				Comment: Likely done.		is judged that this would not influence outcomes						in pre-specified way.		

If study methodology did not explicitly state allocation was randomized, then it was deemed ‘high risk’ of bias for allocation concealment. Only those studies using central randomization, sequentially numbered drug containers or sequentially numbered, opaque, sealed envelopes were deemed ‘low risk.

4.5 Discussion

The aim of this review was to synthesise the available evidence for inter-individual variation in weight change following an exercise-focussed intervention. This is the first systematic review and meta-analysis designed to address this specific aim. It was found that the evidence is limited for clinically relevant 'true' inter-individual variation in weight change in response to an exercise intervention, once the random variability in weight over time in the control group is accounted for. Also, the observed pooled inter-individual response variability, when compared to the pooled mean change in weight was small. The prediction interval ranged from small negative (more response variability in control group) to small positive (more variability in the exercise arm), revealing that the magnitude of the true individual response variability in a future study in similar settings is unlikely to be clinically important. Similarly, the prediction interval for the mean weight loss ranged from moderate reduction to trivial weight gain, indicating that the magnitude of mean weight loss in a future study in similar settings was only possibly clinically relevant.

4.5.1 Aerobic Training Interventions

Aerobic training has been reported to provide positive changes in body mass and body composition (Glowacki *et al*., 2004, Boutcher, 2011). In the current review, three studies were designed to investigate the effect of aerobic training interventions on weight loss, amongst other outcomes (Church *et al*., 2009, Tan *et al*., 2012, Donnelly *et al*., 2013). Although all three studies showed greater variability of changes in weight in the intervention arm, only one showed substantial true individual response variability. As part of the large-scale Mid-West Exercise Trial 2 (MET-2), a control sample (*n*=18) were compared with groups engaging in 5 days per week of aerobic exercise eliciting 400 Kcal (*n*=37) and 600 Kcal (*n*=37) of energy expenditure per session [58]. While group means showed substantial changes in body weight (400 Kcal: -3.9 kg, 600 Kcal: -5.2 kg, control: 0.5 kg), greater variability of changes (SD) was observed in the two intervention groups (400kcal: 4.9 kg, 600kcal: 5.6 kg, pooled SD: 5.27 kg) than in the control sample (3.5 kg). The SD for individual response for this study was therefore 3.9 kg (95% CI, 1.8 to 5.3 kg). The individual response variability in this study is clearly clinically relevant: 2 ×

SD for individual response > minimal clinically important difference for the lower confidence limit. Indeed, the true individual response variance in this study was at least 7-fold greater than any other included study. Nevertheless, removal of this study from the meta-analysis had no material effect on the pooled SD for inter-individual variation in response (0.7 kg, vs. 0.8 kg with all studies included), and a negligible effect on the heterogeneity. This finding is due in part to the low weight afforded to this study in the analysis – just 1.03% - primarily due to relatively small sample size. Similarly, in the large-scale Dose Response to Exercise in Women DREW study, whilst some individuals did not meet their predicted weight loss targets, almost identical variation was observed when participants were randomized to either 4 kcal/kg/week exercise (*n*=139, 3.6), 8kcal/kg/week (*n*=85, 3.5) or 12 kcal/kg/week (*n*=93, 3.4) and when pooled (n= 316, 3.5) when compared to the control sample (*n*=139, 3.37) (Church *et al*., 2009).

4.5.2 Resistance Training Interventions

The effects of concurrent training on body composition are equivocal. Weight gain (Glowacki *et al*., 2004, Dolezal & Potteiger, 1998) has been reported, but positive changes in other measures such as increased fat free mass (Dolzeal & Potteiger, 1998, Binder *et al*., 2005, Hoffman *et al*., 2006) and reduced body fat (Dolzeal & Potteiger, 1998, Glowacki *et al*., 2004, Hoffman *et al*., 2006) have also been described.

Three of the included papers were designed to investigate the effects of resistance training on body weight (Prabhakaran *et al*., 1999, Schmitz *et al*., 2002, Teixeira *et al*., 2003). Of these, one study showed a larger SD of body mass changes over 15 weeks of resistance training in intervention versus control (Schmitz *et al*., 2002). This study reported trivial increases in mean body mass in both groups (Exercise: 0.54 kg, Control: 0.49 kg). The SD of the changes was 1.87 kg in intervention vs. 1.82 in control, resulting in a trivial SD for individual response of 0.4 kg.

In a similar manner to that reported in the previous chapter, two studies reported greater variation in the control sample than in the intervention group. One study investigating the effects of a one year RT intervention on women with and without hormone replacement therapy reported between group mean differences (Texeira *et*

al., 2003); however, whilst weight change was small (EX (with HRT/without HRT) -0.2/0.34kg, CON (with HRT/without HRT) 0.8/-0.4kg) analysis of pooled SDs revealed more variation in the control sample than the intervention (CON - 3.05, RT - 2.55).

The second study (Prabhakaran *et al*., 1999), whilst investigating the effects of 3xRT per week, reported weight gain (0.49 kg) in RT, compared to -0.7 kg in CON. Analysis of the SD of the change score again revealed more variation in the control than the intervention sample (CON – 2.01, RT – 1.35). It appears from analysis of the SD of the change scores that in response to a resistance training intervention, greater inter-individual variation in the control group than in the intervention group is apparent. From these studies, it appears that body weight is not a robust outcome measure for a resistance training. Changes in body composition may be a preferential approach.

4.5.3 Separate Aerobic and Resistance Training Interventions

A single paper reported upon the impact of separate training modalities (Donges *et al*., 2010). Changes in fat mass and lean mass in a control sample (*n*=26), compared to two intervention groups comprising of resistance training (RT) (*n*=35) and aerobic training (AT) (*n*=41), were investigated over 10 weeks. Between group differences in change in body mass were observed, with aerobic training losing body mass (-0.8kg), while both resistance training (0.8kg) and control samples (0.6kg) both increased body mass. The SD of the change in body mass was 1.3 kg in control, 1.5 kg in resistance training, and 1.9 kg in aerobic training (pooled intervention SD of changes = 1.89 kg). The SD for individual response in this study was therefore 1.4 kg, representing small individual response variability.

4.5.4 Combined/Concurrent Training

The effects of concurrent training on body composition are equivocal. Weight loss (Libardi, 2012) and weight gain (Glowacki *et al*., 2004) have been reported, but other health outcomes are often also positively influenced (Dolezal & Potteiger, 1998). Five studies included in the present review were designed to examine the

effects of combined or concurrent aerobic and resistance exercise protocols (Lockwood *et al*., 2008, Burtscher *et al*., 2009, Vilela *et al*., 2015, Baillot *et al*., 2016, Dalager *et al*., 2016).

As part of the Pre-Surgical Exercise Training (PreSET) trial, 30 pre-bariatric surgery participants were randomized to concurrent training (*n*=15) and control sample (*n*=14) for a twelve-week intervention period (Baillot *et al*., 2016). Whilst the intervention group undertook 80 minutes of exercise, three times per week, no statistically different changes in weight loss were observed (CON -0.3, INT -0.92). However, greater variance was observed in the control sample change score SD (4.72) vs the intervention (3.55). Greater mean weight loss was observed in the intervention group (-2.58 kg) compared to a control group (0.79 kg) in a smaller study (Burtscher *et al*., 2009) than added 2 one hour combined aerobic and circuit-type sessions per week for 12 months. Nevertheless, once again greater variance was observed in the control sample change score SD (4.93) vs the intervention (4.12).

In a workplace-based study, 60 participants were randomized to control (*n*=30) or a Workplace Fitness and Education Program (WFEP), consisting of five fifteen-minute sessions per week, alternating muscular endurance and sporting activities (*n*=30) (Vilela *et al*., 2015). No change in body mass was reported for the intervention group, whilst the control group gained a mean weight of 0.4kg. The observed variance was identical in both groups (2.6)

As part of a larger study, combined resistance and aerobic exercise was compared with control and exercise over a ten-week period (Lockwood *et al*., 2008). Whilst a second exercise condition with supplementation were excluded from my review, the two observed conditions reported identical body mass changes (-0.3) and slightly greater SD of the changes (INT 1.9 vs CON 1.6).

Clinically relevant individual response variability was present in just one trial of an intervention involving 12 months of 1 hour per week combined aerobic and circuit-style training (*n*=89), alongside recommendations to undertake 30 minutes of exercise, 6 days per week, compared to a non-exercise control group (*n*=194) (Dalager *et al*., 2016). Mean weight change was -0.49 kg in the intervention group

vs. 0.08 kg in control, with SD of the changes of 3.32 and 2.97 kg, respectively. The SD for individual response was therefore 1.5 kg.

4.5.5 Limitations

I synthesised 12 studies involving a total of 1500 participants. Small sample size is common in supervised exercise-based intervention trials (Keating *et al*., 2017), but this review included 4 larger (*N*=>100) studies (Church *et al*., 2009, Teixeira *et al*., 2003, Donges *et al*., 2010, Dalager *et al*., 2016). Six studies recruited fewer than 20 participants for one or more of the groups (Prabhakaran *et al*., 1999, Lockwood *et al*., 2008, Burtscher *et al*., 2009, Tan *et al*., 2012, Donnelly *et al*., 2013 Baillot *et al*., 2016), and might be prone to small study bias at the individual study level.

I restricted the search to RCTs incorporating exercise-only interventions; included studies differed by exercise mode, intensity, frequency and duration, and length of intervention. This intervention heterogeneity might influence mean effects and/ or individual response variance. There are too few studies to compare the effects in, for example, aerobic versus resistance versus combined interventions.

Given the substantial heterogeneity of the true individual response variance, I derived and presented a prediction interval capturing the plausible range for the true individual response variability, consistent with the data and model, in a future study in similar settings. The prediction interval has been described as providing "potentially the most relevant and complete statistical inferences to be drawn from random effects meta-analyses" (Higgins *et al*., 2009). However, I must exercise due caution in inferences drawn from the prediction interval given the coverage issues identified in the simulations recently conducted (Partlett and Riley, 2017), where these authors reported that the coverage of the interval was particularly poor in cases of low effect heterogeneity and/or markedly variable sample size. With the specific combination of number of studies, between-study heterogeneity of individual response variance and mixture of study sizes in the current review (with REML and Knapp-Hartung estimation) these simulations indicate a maximum under-coverage of the derived prediction interval of 1%. Such under-coverage would have no material effect on the derived probability of individual response variance in a future trial

being clinically relevant. However, I still consider it prudent to view the prediction interval as approximate, as recommended by Partlett and Riley.

Where multiple exercise arms were present in a study, these were combined to avoid double counting of the control arm. This may obscure the effect of different exercise doses; however, analysis of each individual exercise condition vs control, revealed no material difference in individual response variability.

In advance of the study, I proposed various potential effect modifiers (moderators) to account for heterogeneity in individual response variance, including baseline body weight, age, and sex. However, I elected not to conduct any secondary meta regression analyses, as I only had access to study-level covariates (e.g., mean baseline weight, mean age, and proportion of males/females). This type of analysis has been described as 'daft'(Fisher *et al*., 2017), as it has a high risk of ecological bias (Petkova *et al*., 2013); the 'deft' approach advocated by Fisher *et al*. requires either study level analysis of the effects of putative effect modifiers (e.g., treatment interaction effects with sex, age, weight etc.), or an individual-participant data meta-analysis, with relevant interaction terms included in the model. However, obtaining individual participant data from study authors would likely prove to be a major undertaking in this, or indeed any, review. This contention is underscored by the difficulties I experienced in communicating with authors merely to obtain a simple standard deviation of change scores from the data.

Additionally, the energy expenditure induced by the exercise interventions undertaken in the included studies – and whether this would be sufficient, in theory, to induce weight loss above the minimal clinically important difference – is unknown. Whilst beyond the scope of this systematic review and meta-analysis, it is therefore unknown what effects exercise protocols with larger energy expenditures would elicit.

To make inferences in the current study I adopted a threshold for the minimum clinically important weight loss of 2.5 kg – the smallest threshold of absolute weight loss for clinical benefit previously reported (Jensen *et al*., 2014). Those who disagree

with this choice may consider the reported prediction intervals in relation to their own belief in the minimum clinically important difference to make inferences.

Whilst it is beyond the scope of this study to speculate, given the lack of exercise training quantification, such as adherence rates and fidelity it is unknown as to what impact this and other factors such as baseline activity/weight status may have impacted these findings. Future studies may look to include these outcomes in order to fully quantify the training response.

I acknowledge that 20 possibly eligible studies were excluded due to their authors not providing the data requested by e-mail communication. I must, however, assume that these studies are missing at random, as I have no reason to believe that authors would withhold data pertaining to response variance.

4.5.6 Findings in Relation to Current Recommendations and Future Research Directions

This is the first systematic review to focus on the true inter-individual variation in weight loss in response to exercise interventions. I conducted a comprehensive literature search over 14 databases. Evidence in relation to the inter-individual response to various treatments/ interventions is growing rapidly. However, based on the findings of this systematic review, I find limited evidence for the presence of clinically important 'true' inter-individual variation in body mass in response to exercise training. Therefore, further investigation of underpinning mechanisms is likely not warranted, as the prediction interval reveals that individual response variance in a future study in similar settings is unlikely to be clinically important. A caveat here, as acknowledged above, is that I only synthesised 12 effects from heterogeneous exercise interventions. If individual differences in response to interventions targeting body weight are considered important from a precision medicine standpoint, then future randomised trials should be sufficiently sized to afford adequate precision of estimation for both mean intervention effects and the SD for individual responses. The latter would require at least 4× the sample size required to define the mean intervention effect with adequate power and precision, and even larger samples if individual response variance is trivial-small.

4.5.7 Conclusions

To date, much of the research claiming to show substantial inter-individual differences in response to an exercise intervention has been conducted in the absence of a suitable comparator sample (King *et al*., 2008, Cauldwell *et al*., 2009, Cauldwell *et al*., 2013). To quantify the true inter-individual response to an exercise intervention, studies should include a comparator arm, preferably in a randomised controlled trial. Future work should employ this research design and incorporate sound statistical quantification of the response variance in each arm, combined with a threshold for the minimal clinically important difference, to determine the presence of clinically important individual variation in response. In summary, my findings constitute limited evidence for the notion of substantial inter-individual differences in weight loss responses to exercise interventions; individual response variability in a future trial in similar settings is unlikely to be clinically important. These findings, if replicated, confirmed, and extended, might prevent researchers wasting valuable resources searching for explanations of treatment heterogeneity that does not exist or is clinically trivial.

Chapter 5: A Secondary Analysis of Data from the PREMIER Study

5.1 Preface

Elevated blood pressure and increased body mass are important risk factors for diabetes, cardiovascular disease and some cancers, making lifestyle interventions to improve these markers especially relevant. There is purported to be substantial inter-individual differences in how blood pressure and body mass respond to lifestyle/exercise interventions, but studies often lack the comparator data and associated analyses necessary for robust inferences. Recently, an appropriate approach for quantifying these inter-individual differences was described (Atkinson & Batterham, 2015, Hopkins, 2015). Therefore, I aimed to quantify inter-individual differences in the responses of weight loss and blood pressure to lifestyle intervention. Data from the PREMIER Trial were analysed, to quantify the effects of the DASH diet in combination with established treatment (ED) as well as established treatment (E) on systolic blood pressure (SBP), diastolic blood pressure (DBP) and weight loss in comparison to a comparator/advice group.

5.2 Introduction

5.2.1 Elevated Blood Pressure and Cardiovascular Disease Risk

Elevated blood pressure is a common risk factor for cardiovascular disease (Appel *et al*., 2003). Lifetime risk of developing hypertension has been reported to be approximately 90% (Vasan *et al*., 2002), but even above-optimal blood pressure that is not classified as hypertensive can increase the risk of cardiovascular disease (Vasan *et al*., 2001). Current recommendations for the prevention and treatment of high blood pressure have placed an emphasis upon lifestyle modification (Whelton *et al*., 2002), such as weight loss, reduced sodium intake, increased physical activity and limited alcohol consumption. Reductions in SBP and DBP of ≥2 mm Hg can substantially reduce the incidence of CVD in both hypertensive and normotensive individuals, and therefore small reductions of this magnitude are considered clinically meaningful (Turnbull *et al*., 2003), whilst, a 5 mmHg reduction in systolic BP in the population would be predicted to result in a 14% overall

reduction in mortality due to stroke, a 9% reduction in mortality due to coronary heart disease, and a 7% decrease in all-cause mortality (Whelton *et al*. 2002). Given the burden these diseases create upon the healthcare community, it is clear that interventions to reduce this risk are required.

5.2.2 Gender Differences in Blood Pressure

In general, men are reported to have higher blood pressure than women through middle age (Burl *et al*., 1995). Furthermore, the incidence of uncontrolled hypertension is also greater in men than in women (Anastos *et al*., 1991), possibly due to the role played by testosterone (Reckelhoff, 2001).

5.2.3 Impact of Weight Change

Obesity and other comorbidities continue to increase among both sexes (Mokdad *et al*., 2003). The impact of obesity remains considerable, with associated health risks conferring increased likelihood of the development of diabetes (Mokdad *et al*., 2003), hypertension (Huang *et al*., 1998, Mokdad *et al*., 2003), cardiovascular disease (Poirier *et al*., 2006) and metabolic syndrome (Despres *et al*., 2008). It has also been suggested that dietary modification by itself reduces the risk of secondary myocardial infarction by about half in patients with coronary disease (de Lorgeril *et al*., 1999). Williamson *et al*. (2018) adopted a threshold for the minimum clinically important weight loss of 2.5 kg – the smallest threshold of absolute weight loss for clinical benefit previously reported (Jensen *et al*., 2014). Given this information, further efforts should focus on the prevention and treatment of overweight individuals through measures to prevent and reduce the burden of ill health, such as dietary modification and increased physical activity/ exercise.

5.2.4 Use of the DASH Diet

The Dietary Approaches to Stop Hypertension (DASH) trial was a randomized, multicentre, comparing the effect on blood pressure of 3 dietary patterns: control, fruits and vegetables, and combination diets, with patterns differing in selected nutrients hypothesized to alter blood pressure (Karanja *et al*., 1999). Application of the DASH diet as an intervention has previously been reported to contribute to

reduced blood pressure (Stacks *et al*., 2001a, Svetkey *et al*., 2005), with greater improvements in vascular and autonomic function than advice alone (Blumenthal *et al*., 2010) and lowering of both LDL and total cholesterol (Obarzanek *et al*., 2001).

5.2.5 Inter-Individual Variation in Response

Interest in the concept of individual responses to exercise interventions has been growing over the last 30 years (Prud'homme *et al*., 1984, Despres *et al*., 1984, Lortie *et al*., 1984, Rose & Parfit, 2007, Bouchard *et al*., 2015, Mann *et al*., 2014) and it has been postulated, for example, that the benefits of physical activity may vary between age and gender groups (Peterson, 2007). Most public health and exercise research focuses upon mean group changes (Bouchard & Rankinen, 2001), but these may hide a wide range of responses (Karavirta *et al*., 2011) and do not allow us to distinguish the inter-individual variation in response (Senn, 2004). 'True' inter-individual differences in the response to an intervention are less frequently reported, even though it has been proposed that there is large inter-individual variability in response to physical activity interventions (Prud'homme *et al*., 1984, Despres *et al*., 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Hamel *et al*., 1986, Simoneau *et al*., 1986, Bouchard & Rankkinen 2001, Hautala *et al*. 2003).

Importantly, even in the studies in which inter-individual differences in the response to exercise training are considered, concerns have been levelled at the designs and analysis approaches in these investigations (Hopkins, 2015, Atkinson & Batterham, 2016, Williamson *et al*., 2017). It has recently been described how the key trigger for further investigation into inter-individual responses is when the standard deviation of change (SD_{change}) in the intervention sample is substantially larger than the same standard deviation derived from a suitable comparator sample (Hopkins, 2015, Atkinson & Batterham, 2016, Williamson *et al*., 2017). Only when inter-individual variations in response are quantified, using the equation $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$ (showing larger variation in the SD_{change} in an intervention group vs a control group), should further investigations into possible mediators of response be undertaken.

To this end, it was my intention to carry out a detailed and rigorous secondary analysis, using the methodology recently described (Hopkins, 2015, Atkinson & Batterham, 2015, Williamson *et al*., 2017) of the data collected during the PREMIER Trial, to correctly quantify the 'true' inter-individual variation in weight loss and blood pressure response.

5.3 Methods

5.3.1 The PREMIER Trial

The PREMIER research design and rationale has previously been published (Svetkey *et al*., 2003). It was a multicentre randomized study, targeted at generally healthy adults (*n*=810), aged 25 years or older, with a body mass index of 18.5 – 45, and with above optimal blood pressure. The study was aimed at identifying the effect of an established intervention (a behavioural intervention that implemented traditional lifestyle recommendations such as weight loss, reduced sodium intake, increased physical activity and limited alcohol intake, *n*=268), and established intervention plus DASH diet (the same as the 'established' group, with the addition of dietary goals and strategies to achieve weight loss through implementation of the DASH diet, *n*=269) against an advice only group (who received a single, 30 minute individual discussion session with an interventionist, typically a registered dietician, following randomization, *n*=273). The sample size in the PREMIER trial was large, and the trial was powered (90%, *p*=0.05) to detect a difference in blood pressure between arms of 1.6-1.8 mmHg. However, the trial was not powered to detect interactions (e.g. sub-group effects) of the same magnitude, as this would require four times the sample size required to detect the overall main effect (the 'rule of 4').

Baseline characteristics including age, blood pressure, height, body mass were all measured, and no substantial differences between arms were observed at baseline. Blood pressure was obtained by trained, certified individuals, where, following 5 minutes rest, the observer measured blood pressure in the right arm, with systolic blood pressure defined as the appearance of the first Korotkoff sound, and diastolic as the disappearance of the Korotkoff sounds (Appel *et al*., 2003).

5.3.2 Statistical Analysis and Results

The present investigation was run in three parts. The first was determined to be a reproducibility analysis, whereby I attempted to reproduce the original published results for systolic blood pressure (SBP), diastolic blood pressure (DBP) and weight change (Appel *et al*., 2003), by running the same analysis reported by the authors. Analyses were conducted using SPSS software (v23, IBM, New York, United States), with change in outcome from baseline to 6-months as the dependent variable, and intervention arm, clinical centre/cohort, and the raw baseline measurement of each variable as independent variables using a linear mixed model with random intercepts for subject.

The published point estimates and 95% confidence intervals for the differences between trial arms in the change from baseline to 6 months were reproduced successfully for all outcomes (Appel *et al*., 2003). This is a crucial first step in advance of any more nuanced secondary analysis, as it provides confidence in the integrity of the raw data.

To investigate the 'true' inter-individual variation in response, a linear mixed model was again used. The advice only group (control) provided the counterfactual for both men and women, allowing for the observation of response variance in the intervention over and above that seen in the control.

I derived the SD for true individual responses using an extension of the method described in Atkinson and Batterham (2015). As there are two intervention arms (each versus control) two dummy variables are required - XVAR1 and XVAR2 – to allow for and quantify additional response variance in each intervention versus control. The XVAR1 variable has a score of '1' when coincident with the Established group and '0' otherwise, whereas XVAR2 had a score of '1' when associated with the Established+DASH (ED) arm and '0' otherwise. In a linear mixed model, the change in outcome from baseline to 6 months was the dependent variable, with sex, clinical centre/ cohort, and baseline value of the outcome as fixed effects. The two dummy variables were included as random slopes with no intercept. Using this approach, for SBP, the mean changes were E -3.7 (90%CI -5.3 to -2.1)

mmHg, ED –4.3 (-5.9 to -2.8) mmHg versus advice only. The SD_{IR} for E vs advice was 4.4 (1.3 to 6) mmHg, compared to ED vs advice of 3.4 (-2.2 to 5.3) mmHg. For DBP, the mean changes were E -1.7 (-2.8 to -0.6) mmHg, ED –2.6 (-3.7 to -1.5) mmHg versus advice only. The pooled SD_{IR}s were 2.1 (-1.9 to 3.5) mmHg and 2.6 (-1.3 to 3.9) mmHg for E vs advice and ED, respectively. Given that we double these SD_{IR}s before evaluating its magnitude to reflect a comparison between a typically high (mean + SD_{IR}) and typically low (mean – SD_{IR}) responder (Hopkins, 2015), if the MCID is 2 mmHg, then a moderate effect is 3x this = 6 mmHg, and a large effect is 6x this = 12 mmHg. Therefore, when compared to a relevant MCID of a 2-3 mmHg reduction (Turnbull *et al*., 2003), these results (E $2*SD_{IR}$=4.2, ED $2*SD_{IR}$=5.2) indicate small-moderate inter-individual variation in response.

For weight change, the mean weight loss was -3.5 kg (90% CI -4.2 to -2.7) kg in E versus advice only and -4.2 kg (-5.0 to -3.4) in ED versus advice only. The pooled SD_{IR} for E vs advice was -4.3 (3.7 to 4.8) kg, compared to ED vs advice of -4.5 (4.0 to 5.0) kg.

The second part of the investigation was to investigate the impact of sex on the 'true' inter-individual variation in response to the treatments; that is, does sex account for any of the observed treatment heterogeneity? The linear mixed model approach was utilised again, although this time a sex-by-treatment interaction was included. This interaction term quantifies the difference between men and women in the mean effect of the intervention versus control. For SBP, male SBP reduced in E versus advice by 4.7 (95% CI -7.3 to -2.1) mmHg and females reduced by 3.1 (-5.1 to -1.2) mmHg. Men therefore have a greater response in E versus advice than women by 1.6 (-1.7 to 4.8) mmHg. In ED versus advice, males reduced SBP by 5.6 (90%CI -8.1 to -3.2) mmHg and females reduced by -3.5 (-5.5 to -1.5) mmHg, resulting in a 2.1 (-1.0 to 5.3) mmHg mean difference in response between men and women following ED.

The sex-by-treatment interaction would be expected to explain at least some of the observed individual response variance, leading to a reduction in the SD for individual responses when the interaction is included in the model. However, this was not the case. When sex-by-treatment was added to the model, the SD_{IR} for E vs

advice remained -4.4 mmHg, compared to ED vs advice of -3.4 mmHg. For DBP, the SD_{IR}s once again remained essentially unchanged. The SD_{IR} for E vs advice was -2.0, compared to ED vs advice of -2.6 mmHg. For weight change, a similar phenomenon was evident. When sex-by-treatment interaction was added to the model, a difference of 1.8 kg between men and women was observed for ED, compared to 1.2 kg in E. The SD_{IR} for both intervention arms was effectively unchanged (4.3 kg vs 4.5 kg).

The fact that sex does not explain any of the observed individual response variance, even though there is a difference in mean response between the genders, is paradoxical, as it cannot be the case that a substantial sex-by-treatment interaction does not account for some of the observed overall treatment heterogeneity. To that end, further analysis was undertaken, to try to elucidate this paradox. The third part of the analysis was to model the data separately, with the dataset split by gender. The same statistical model described above was applied, but of course with the sex-by-treatment interaction removed. For men, in E, the SD_{IR} was 6.2 (90% CI 2.9 to 8.3) mmHg, compared to 5.7 (2.4 to 7.7) mmHg in ED. For women, in E, the SD_{IR} was 3.1 (-2.8 to 5.6) mmHg, yet in ED alone, the SD_{IR} was -1.3 (-4.8 to 4.5) mmHg. This indicates a magnitude of 'true' inter-individual variation in response that is vastly greater in men than that observed in women, and that there is more inter-individual variation in response in the advice group than ED in women. The SD_{IR} is also greater than the mean effect. Therefore, it appears that in SBP, the overall SD_{IR} overestimates female SD_{IR} and underestimated male SD_{IR}.

For DBP, when split by sex, a slightly different trend occurs. In men, in response to E and ED, SD_{IR}s are 1.5 (90% CI -3.4 to 4.1) mmHg and 3.9 (-0.9 to 5.5) mmHg respectively, whilst in women, they are 2.2 (-2.2 to 3.9) mmHg and 1.2 (-2.9 to 3.3) mmHg respectively.

When split by sex, inter-individual variation in weight change followed a similar trend to SBP. The observed variance was approximately double in men than in women. For men, in response to E and ED, SD_{IR} was -4.9 (4.0 to 5.7) kg and -5.5 (4.6 to 6.2) kg respectively. This was approximately double the amount presented as an MCID in Chapter 4. When interpreting the SD for individual responses we double

it, therefore these individual responses are classified as moderate. In women, SD_{IR} was -3.8 (3.1 to 4.5) kg and -3.7 (2.6 to 4.3) kg for E and ED respectively.

5.3.3 Individual Prediction Interval for a New Participant

As a novel method, I propose that the individual response variance derived from an RCT may be used to construct a 95% individual prediction interval. This interval provides a plausible range for the response of a new participant undergoing the same intervention in a similar setting, versus what would have happened to this participant had they not engaged in the intervention (the counterfactual). The approach I have taken mirrors the method used to derive a prediction interval for a new study in a random effects meta-analysis (IntHout *et al*., 2016). As an example, consider the effect of the Established plus DASH intervention versus advice only in men. The mean effect was a reduction in systolic blood pressure of 5.6 mmHg, with a standard error of 1.235, and a SD for individual responses of 5.7 mmHg. The standard error (SE) for the individual participant prediction interval is given by:

$SE = \sqrt{}(1.235^2+5.7^2) = 5.83.$

The next step is to multiply the SE by the appropriate value from the t distribution (1.971) for a 95% interval for the degrees of freedom (211) for this effect: 5.83 × 1.971 = 11.5. The 95% prediction interval is then derived as the mean change minus 11.5 to the mean change plus 11.5:

-5.6-11.5 to -5.6+11.5 = **-17 to 6 mmHg**.

Given the substantial observed treatment heterogeneity in men, the plausible range of effects for a new male participant undertaking the Established plus DASH intervention (versus a hypothetical control) spans moderate harmful (+6 mmHg; increased systolic blood pressure) to a large beneficial effect (-17 mmHg). It is then straightforward to estimate the probability that a new male participant would benefit from the intervention by at least the minimum clinically important difference (MCID) of 2 mmHg. The *t* value required to derive this probability is given by the observed mean effect minus the MCID, divided by the SE of the prediction interval:

(5.6-2)/5.83 = 0.617. The area under the *t*-distribution to the left of 0.617 is 0.73. Therefore, the probability (% chances) that a new male participant undergoing this intervention would benefit is 73%, or odds in favour of benefit of almost 3:1. Using the same method, for a new male participant the probability of an *increase* in blood pressure post-intervention of >2 mmHg (the MCID) is 10%, and there is a 17% probability of a trivial change (within ± the MCID). These findings imply that around 7/10 new individuals would derive beneficial reductions in systolic blood pressure as a result of such an intervention, 1-in-10 would get worse, and 2/10 would experience no substantial change. These values are an average, with a confidence interval, which are subject to the uncertainty in the SD_{IR}. Of course, further research is required to help explain the marked individual response variance in men and to identify the characteristics of participants most likely to benefit. For example, intervention fidelity is probably an important mediator of treatment effect, but no detailed data are available on this variable.

5.4 Discussion

My aim was to carry out secondary analysis of the data collected during the PREMIER trial, in order to correctly quantify the 'true' inter-individual variation in weight change and blood pressure response to advice only, established care and established care plus the DASH diet. The key findings were that there are large SBP and weight loss individual responses for men but not for women, and that an interesting paradox regarding the distribution of the 'true' inter-individual variation in responses was observed.

5.4.1 Initial Exploratory Observation of Response Variance

The SD for the raw SBP change scores was 9.9 mmHg in the intervention vs. 9.2 mmHg in advice only. However, it is a flawed approach to think in SD units rather than variance and therefore assuming trivial IR. To explain fully, SQRT (9.9^2-9.2^2) is 3.66 mmHg, which is substantial. On initial appraisal, there initially appears to be a trivial difference in SDs (9.9 vs 9.2). However, when you have SDs of this magnitude, squaring them magnifies the difference between them (i.e. 98.01

vs 84.64), versus the same difference in SD_{change} of 0.7, with a smaller overall SD, for example 1.7 (2.89) in one group and 1.0 (1) in the other. This highlights the additional need to think in terms of differences in response variance, and then express the individual response variability as an SD.

5.4.2 Systolic Blood Pressure

The original PREMIER trial was reported to reduce blood pressure, thereby reducing prevalence of hypertension in the cohort (McGuire *et al*., 2004), suggesting that the DASH diet had numerous possible health benefits. The DASH diet has also previously been reported to substantially reduce blood pressure (Stacks *et al*., 2001a, Stacks *et al*., 2001b).

The value of 11.99 mmHg for the individual response variance, calculated from the original raw PREMIER data, thereby giving an SD_{IR} of 3.4 mmHg, from the full sample analysis is 'false'. This led to an inability to explain or account for any of the variance when a sex by treatment interaction was entered in the model; the explanatory effect of the mean difference between sexes for the effect of treatment is actually offset by the large difference in response variance in men vs. women.

This finding also applies to the raw change scores in men and women for both the treatment arms and the control, where the SD of the changes in women is larger for advice only than for ED. This phenomenon is only fully observed when sex-by-treatment group interaction is entered in the model. The mean difference (point estimate) in the effect of the treatment in men vs. women is substantial and should therefore show up as individual responses that would then have attenuated when a sex-by-treatment interaction was entered into the analysis. If a linear mixed model were run without this interaction, substantial individual response variance would be evident. When the model has the interaction term added, this variance will disappear, or reduce, based upon the extent to which sex explains that portion of variance.

It is usually the case that substantial interaction terms cannot be present without observing a large inter-individual variation in response that is then at least partially explained by the interaction term. However, in this case, it does not explain or

account for any of the 11.99 mmHg individual response variance. In practice, if there are independent groups (such as sex), then separate analyses should be undertaken early in the process, in order to identify the presence of such a phenomenon. This is highlighted by the fact that the value of 11.99 mmHg, derived from the full model for the individual response variance, does not accurately apply to either men or women in this case, and therefore cannot be explained by any available moderators.

Practically, these observed SD_{IR} are large, when compared to a minimal clinically important difference (MCID) of 2-3 mmHg for reducing mortality (Turnbull *et al*., 2003). When we double the SD_{IR}, as is required to evaluate the individual variation in response to a clinically anchored MCID, the magnitude of individual variation in response is actually 3-4 times the size of the relevant MCIDs.

5.4.3 Diastolic Blood Pressure

Non-significant differences in DBP have been reported between both men and women (Jaquet *et al*., 1998). In the present secondary analysis, a mean difference in reduction of DBP of 2 mmHg was observed between men and women, with men showing, on average, a greater mean change. However, a divergent trend was evident in inter-individual variation; the observed SD_{IR} was smaller in men in ED than women, whilst conversely, women had smaller SD_{IR} in E only, compared to men. The observed inter-individual variation in DBP were of a magnitude of 0.75 to 1.9 times the MCID (2 mmHg), indicating that these variations in response may be of clinical significance.

5.4.4 Weight Loss

Previous research has reported larger reductions in blood pressure with DASH or DASH with weight management (calorie restriction of 500 kcal) than those reported in the PREMIER Trial (Blumenthal *et al*., 2010). This may be as a result of the weight manipulation through calorie restriction, the addition of supervised exercise, or the comparatively small sample size (n=144) inflating the effect of the intervention. In the PREMIER dataset, whilst similar mean responses were observed for weight loss, the same phenomenon was observed as for SBP. The observed true

individual response variance in men was almost double that observed in women, leading to substantially greater SD for individual responses in men. These were of a much greater magnitude of those suggested in Chapter 4 (2.5 kg), at a conservative estimate, to confer positive health benefits, indicating moderate inter-individual variation in response. In addition, these data show that diet may confer more positive benefits than exercise for weight loss, with a greater effect observed in this analysis, compared to those previously reported (Williamson *et al*., 2018).

5.5 Conclusions

When analysing the original PREMIER trial dataset, there is 'false' observed overall individual response variability for SBP and weight change, due to the presence of zero/ negative individual response variance in women, but very large inter-individual response variance in men. Whilst the effect in women is relatively consistent and in men much more variable, the individual response variance for SBP (11.99 mmHg) estimated from the whole sample does not apply well to either men or women, underestimating men and overestimating women. This is why including the sex-by-treatment interaction did not explain any of the overall SD_{IR}, as virtually all of the individual response variance is in men not women. Women appear to be more consistent responders to the intervention than men, for some reason. The reason for this is unknown, but could, speculatively, be due to be higher intervention fidelity in women, whereby they listen to, and follow instructions, with greater accuracy than men.

Therefore, putting a sex-by-treatment interaction in the model for this dataset does not account for any of the 'true' inter-individual response variance for SBP or weight change. This finding arises due to the 'overall individual response variance being false. The vast difference in individual response variance between men and women completely overwhelms and offsets any reduction in the 'pooled' individual response variance when the sex-by-treatment interaction is included in the model, making it appear that sex is not a moderator of the individual response variance.

This issue should provide a cautionary tale and a recommendation to all researchers doing these types of analyses, highlighting a crucial point that the analyses must – at

least initially – be stratified by sex, rather than deriving the overall sample individual response variance, as it may be erroneous, as it is in this instance.

The use of a Prediction Interval for this analysis provides a novel approach to providing a plausible range for the response of a new participant undergoing the same intervention in a similar setting, versus what would have happened to this participant had they not engaged in the intervention. This approach has not been utilised in the secondary analysis of data and, as long as the SD_{IR} and its associated confidence intervals are relatively precise, can reliably predict the likelihood of a positive change being conferred upon an individual in undertaking interventions in future settings, with the caveat that it requires a precise estimate of SD_{IR}.

This secondary analysis of the PREMIER trial data showed much larger inter-individual variations in the response of weight loss and blood pressure control in men to established treatment and established treatment plus DASH diet, when compared to women, of a magnitude 3-4 times the MCID. The findings reinforce the requirement for a suitable comparator sample, as discussed repeatedly in this thesis. It is beyond the scope of this investigation, however, speculatively, these findings may be the result of greater fidelity in women. Additionally, the findings create clear areas for further investigation aimed at better-targeted interventions for subgroups, including the response and reactivity of blood pressure in response to exercise.

Chapter 6: Inter-Individual Differences in Acute Blood Pressure and Heart Rate Response to High Intensity Aerobic Exercise: A Replicate Crossover Design

6.1 Preface

Given the findings of substantial 'true' inter-individual variation in response of systolic blood pressure in response to chronic lifestyle interventions reported in Chapter 5, it is important to identify whether these responses may be present acutely following exercise challenges. Therefore, in this chapter, I aimed to quantify and partition the many possible elements of variation of blood pressure and heart rate response following bouts of high intensity 'aerobic' interval exercise, using a novel replicate crossover trial. The key to this is the use of specific coding for the analysis and partitioning of variance into 'consistent' and 'one-time' inter-individual variation in response.

6.2 Introduction

Blood pressure is the product of cardiac output and total peripheral resistance (Sabbahi *et al*., 2018). High blood pressure, or hypertension, affects approximately 25% of the population (Carpio-Rivera *et al*., 2015), and is the major risk factor for cardiovascular disease (Boutcher & Boutcher, 2017). Chronic exercise is consistently reported to reduce blood pressure (Fagard, 2005, Cardoso *et al*., 2010, Pescatello *et al*., 2004a). However, it has been suggested that this finding may disregard the last bout effect of acute exercise if the measurement is taken close to the preceding exercise bout, which has been shown to reduce blood pressure (post exercise hypotension (PEH)) (Carpio-Rivera *et al*., 2015) in the period 5-60 minutes post-exercise.

6.2.1 Post Exercise Hypotension

The magnitude of hypotension in the post-exercise period is generally greater than observed chronically and lasts from minutes (MacDonald 2002) to hours (Pescatello

et al., 2004b), and differs by time of day (Jones *et al*., 2008), intensity and duration, but not by total work completed (Jones *et al*., 2007). Immediately post-acute exercise, systolic blood pressure usually normalises rapidly, though can also be subject to a large drop due to excessive venous pooling (Le *et al*., 2008), while a decline in acute systolic blood pressure of >10 mm Hg below resting value is associated with increased cardiovascular risk (Dubach *et al*., 1988). However, it is possible that chronic reduction in blood pressure may be due to the contribution of accumulated acute episodes of PEH (Thompson *et al*., 2001). Diastolic blood pressure remains generally unchanged or slightly decreases in normotensive subjects (Palatini, 1988).

6.2.2 Blood Pressure Reactivity

This PEH is preceded by an increase in post-exercise blood pressure – a phenomenon called blood pressure reactivity. Submaximal exercise has been reported to elicit similar cardiovascular responses as those observed via psychological stressors (Lambiase *et al*., 2013). Whilst SBP normally rises during dynamic exercise in response to increased cardiac output (Jae *et al*., 2015), an exaggerated peak SBP reactivity (defined as an increase during exercise testing to ≥210 mmHg (Jae *et al*., 2006)) is an indication to stop any cardiopulmonary testing (Pescatello *et al*., 2014) and is associated with risk of developing hypertension (Matthew *et al*., 1998).

6.2.3 The Mechanisms of Blood Pressure Response

Higher fitness levels appear to elicit a smaller magnitude of heart rate reactivity response (Boutcher & Nugent, 1993), though the mechanisms for this are, as yet, unknown (Lambiase *et al*., 2013). It has been suggested that as exercise elicits norepinephrine release in a curvilinear manner in response to increased workload and in combination with epinephrine (Kaufman & Forster, 1996), these chemical responses may be responsible for the magnitude of the rise in exercise heart rate and blood pressure.

6.2.4 Gender Differences in Response

There are reports that males and females, whilst utilising the same pathways for stress response, appear to differ in response (Huang *et al*., 2013). Males present larger diastolic blood pressure responses to acute exercise, which may suggest that male responses are 'vascular' while female responses are 'cardiac' (Allen *et al*., 1993).

6.2.5 Inter-Individual Differences in Response

Interest in the individual response to a treatment intervention has gathered momentum over the last three decades (Prud'Homme *et al*., 1984, Lortie *et al*., 1984, Hamel *et al*., 1986, Rose & Parfitt, 2007, Senn *et al*., 2011, Bouchard *et al*., 2012, Mann *et al*., 2014, Snyder *et al*., 1997, Barbeau *et al*., 1999, King *et al*., 2008, Barwell *et al*., 2009, Caudwell *et al*., 2009, Caudwell *et al*., 2013), developing interest in the concept of precision medicine – incorporating 'made-to-measure' therapies based on the individual response of a patient (Senn *et al*., 2011). It has been suggested that personalized medicine may revolutionize healthcare through utilization of individual genetic information, thereby improving drug safety and efficacy (Katsanis *et al*., 2008). However, previously reported associations been between genotype and phenotype are often too small to provide sufficient evidence for response or phenotype prediction (Khoury & Galea, 2016).

Most researchers have presented mean data, with inter-individual variation in response often being overlooked (King *et al*., 2012). This focus on mean effects may hide important observations that a fixed dose of exercise may have varying effects upon individuals (Bouchard, 1983, Bouchard & Rankinen, 2001, King *et al*., 2008). It has been suggested that belief in inter-individual variation as the cause of observed variation in treatment response outcomes may be due to lack of rigorous study design (Senn *et al*., 2011).

6.2.6 Partitioning Variance Through the Replicate Crossover

It has previously been described how attempts to quantify the inter-individual variation response to chronic exercise are hampered by a lack of a control sample (Atkinson & Batterham, 2015, Williamson *et al*., 2017). Recent insights have suggested a new approach in order to partition and quantify variance in trials of acute responses: the replicate crossover (Senn, 2016). This method is suggested to allow for the isolation of components of variation corresponding to patient-by-treatment interaction (Senn *et al*., 2011), as replication of both an intervention and a control period allows for an interaction to be determined.

Given the lack of previous investigation into this subject, and in the knowledge that blood pressure reactivity varies with circadian rhythm (Jones *et al*., 2006), it is of interest to investigate the presence of any inter-individual variation in this reactivity. Whilst the replicate crossover method for attempting to partition variance was recently utilised (Goltz *et al*., 2018), no previously published studies have investigated the acute inter-individual variation in blood pressure reactivity to exercise. Additionally, the study by Goltz *et al*. (2017) compared three analysis methods, all of which were different from that proposed by Senn *et al*., (2011). Therefore, in the first replicate crossover design study to quantify inter-individual variability of blood pressure reactivity in response to exercise, the aim of this study was to identify the presence of any 'true' inter-individual variation in post-exercise blood pressure reactivity, measured by systolic and diastolic pressure, and any 'true' inter-individual variation in heart rate response, following repeated acute bouts of high-intensity aerobic intermittent exercise. Within the programme of work for this PhD thesis, this trial serves as a proof-of-concept study, which provided data with which to develop and refine analysis models and code to properly partition the variance and isolate the true individual response variability in acute exercise vs. control. It also serves as pilot testing of the methods, procedures and analysis for future, larger-scale investigations.

6.3 Methods

6.3.1 Participants

As there were six possible exercise sequences, ideal recruitment sample sizes were in multiples of six. The target sample size was 12, representing an adequate sample size for a pilot/ proof-of-concept study using a replicate crossover design. Twelve normotensive, physically active people (4 women, 8 men, age: 29.7 ± 5.2 y, height: 173.9 ± 9.4 cm, body mass: 72.5 ± 11.0 kg, peak oxygen uptake ($\dot{V}O_2$peak) 39.4 ± 8.6 mL.kg^{-1}.min^{-1}) volunteered and were recruited, by showing interest following internal emails and advertisements, to take part in this replicated period crossover design trial. Participants were randomised in blocks of two to one of six possible sequences of 2 control and 2 exercise replicates over four periods. Allocation was concealed from those assessing eligibility and recruiting participants using a statistical advisor. This approach was undertaken to allow the identification of the subject-by-treatment interaction and thus to quantify the heterogeneity in the response to acute exercise. One participant was unable to attend all sessions with the required 72 h separation between trials and was therefore excluded from the experimental protocol, whilst one volunteer was excluded due to medical reasons. Therefore, eleven of the participants completed the study.

Following a full information brief (Appendix 1), participants attended the laboratory on five separate occasions, each separated by >72 h. The first visit was for habituation purposes, completion of informed consent, and measurement of peak oxygen uptake ($\dot{V}O_2$peak). During this session, stature (m) was determined using a stadiometer (Seca, Hamburg, Germany), body mass (kg) was measured using an electronic measuring station (Seca, Hamburg, Germany), resting heart rate (HR) was measured using a wrist worn monitor (Polar FT1, Polar Electro Oy, Finland), paired with a chest-worn strap (Polar T31 coded strap, Polar Electro Oy, Finland). Heart rate was taken in standardised laboratory conditions, with all participants in an upright, seated posture. Resting blood pressure (mmHg) was measured using an automated blood pressure monitor and 22-32cm cuff (Omron M2, Omron, Kyoto, Japan). Using this validated monitor (Topouchian *et al*., 2011, Takahashi *et al.*,

2015), following 5 minutes of complete rest in a supine position, resting blood pressure was taken on the left arm, with the cuff approximately 2.5cm above the elbow crease and the bladder centred over the brachial artery (Frese *et al*., 2011), and was determined from the mean of three measurements.

The final four visits were for completion of the main experimental trials, with two exposures each to the intervention and the control conditions (Senn, 2016). The participants were randomised to one of six possible sequences of trial (C=control, E=exercise), and were informed of the nature of each day's place in that sequence upon arrival:

1. C-E-C-E
2. C-E-E-C
3. C-C-E-E
4. E-C-E-C
5. E-C-C-E
6. E-E-C-C

All exercise was performed on an upright cycle ergometer. Exercise was performed following abstinence from alcohol (24 h), caffeine (12 h) and vigorous exercise (24 h), and all participants were requested to consume a similar diet prior to each attendance.

All participants had no history of major illness, cardiovascular disease, were not taking any medications, and were engaged in habitual physical activity for general health and wellbeing. The study conformed to the declaration of Helsinki and was approved by the Institutional Ethics and Research Governance Committee. All participants were fully informed of the study methods prior to giving written informed consent (Appendix 5). Participant characteristics are presented in Table 6.

6.3.2 Measurement of Peak Oxygen Uptake

Peak oxygen uptake was measured by a ramp test on an electromechanically braked cycle ergometer (Lode Excalibur, Groningen, Holland). The ramp test was selected because exercise test protocols with large stage-to-stage increments in energy

requirements generally have a weaker relationship between measured $\dot{V}O_2$ and work rate (Balady *et al*., 2010). Participants performed 5 minutes of submaximal exercise

Table 6. Participant characteristics

	Recruited (*n*=12)	Analyzed (*n*=11)
Age (yrs)	29.7 ± 4.9	29.7 ± 5.2
Stature (cm)	173.9 ± 10.1	173.9 ± 9.4
Mass (kg)	72.5 ± 12.5	72.5 ± 11.0
Resting SBP (mmHg)	127 ± 10	127 ± 10
Resting DBP (mmHg)	75 ± 7	76 ± 7
Resting heart rate (b.min)	67 ± 21	67 ± 14
$\dot{V}O_2$peak (mL.kg^{-1}.min^{-1})	39.4 ± 8.3	39.4 ± 8.6

(50 W) as a standard warm-up. As the test commenced, beginning with no load, power output increased by 30 W per minute until volitional exhaustion or the subject could no longer maintain a pedal cadence of 70-90 revolutions per minute (RPM). Expired air was collected and analysed throughout (Zan 600 USB CPX, nSpire Health Inc., United Kingdom), whilst heart rate (HR) was monitored at rest and every minute using a wrist-worn monitor and coded chest strap (Polar FT1 and Polar T31, Polar Electro Oy, Finland). $\dot{V}O_2$peak was defined as the peak value of a 5-point average data set, meaning that the data was filtered for any anomalies and then averaged out for every five consecutive data points (Robergs *et al*., 2010). Oxygen uptake was then interpolated to identify the exercise work rate (power output) corresponding to 70% $\dot{V}O_2$peak using linear regression.

6.3.3 Research Design

All participants completed four experimental trials in a thermoneutral environment (18-22°C). Each trial was completed in different sequence, as described above. Participants reported to the laboratory in the morning, and each visit consisted of two phases; the first consisted of 5 minutes of supine rest, which, within the time constraints of the study and the fact that the optimal time at rest before measurement is, as yet, undefined (Sala *et al*., 2006), was considered sufficient to remove the residual effects of prior activity. Following this rest period, resting blood pressure was measured. Based on this selected rest duration, differences in resting time should be taken into account when comparing BP measurements performed in future studies

and in different settings (Sala *et al*., 2006). The second phase was the experimental protocol.

6.3.4 Experimental Protocol

Participants reported to the laboratory in the morning (0830-1130), as changes in post-exercise blood pressure have previously been reported for both continuous (Jones *et al*., 2008) and intermittent exercise (Jones *et al*., 2009), with less marked diurnal differences observed between am and pm exercise following intermittent exercise than in continuous exercise (Jones *et al*., 2009). The experimental protocol consisted of two conditions. The exercise condition (EX) comprised of two 10-min intervals of upright cycling, at the individual's estimated power output at 70% of $\dot{V}O_2$peak, separated by a 5-min recovery period. To ensure that participants' work rate was at the correct intensity, the resistance (Watts) were constant during each exercise bout. A control sample, involving collection of the same data during a period of no exercise, was the second condition. This rest (CON) condition consisted of the same time periods, sat at rest on the upright cycle ergometer.

6.3.5 Blood Pressure Measurements

The blood pressure monitor was fitted to the upper arm in accordance with practical guidelines previously established (O'Brien *et al*., 2005). The mean of three measurements was obtained as the baseline measure. The blood pressure monitor was removed following baseline measurements and participants moved to the cycle ergometer, where they completed EX or CON conditions. Blood pressure was measured during each rest period in EX, and at the same time points during the protocol in CON. These measurements were repeated immediately on cessation of exercise following both 10-minute periods, and at the corresponding time point during the control condition, with the second post-exercise measurement taken as the final measure.

6.3.6 Components of Blood Pressure

Blood pressure has also been reported to consist of pulsatile and steady components (Safar, 1989, Darne *et al*., 1989, O'Rourke, 1982). The pulsatile component, estimated by pulse pressure (PP) represents blood pressure variation and is affected by heart rate (Franklin *et al*., 1997), left ventricular ejection fraction and large-artery stiffness. In contract, the steady component, which is estimated by mean arterial pressure (MAP), is a function of left ventricular contractility, heart rate, and vascular resistance (Safar, 1989, Benetos *et al*., 1997a). Mean arterial pressure has also been suggested as an alternative measurement in patients for hypotension detection (Henry *et al*., 2002).

Pulse pressure is defined as SBP minus DBP (Lloyd-Jones & Levy, 2007), and can be used reliably as a prognostic marker in clinical practice (Yildiran *et al*., 2010). It has been suggested that pulse pressure may become a more important blood pressure measurement that is associated with cardiovascular disease in older adults (Franklin *et al*., 1999). Average SBP, DBP, and MAP have been suggested to strongly predict CVD risk in younger men, whereas average PP is purported to be associated with the risk of CVD in both younger and older men. (Sesso *et al*., 2000). This corresponds with earlier suggestions that a wide pulse pressure is a significant independent predictor of all-cause, cardiovascular and coronary mortality (Benetos *et al*., 1997b).

It has previously been claimed that individuals with lower systolic blood pressure response during exercise testing are at increased risk of adverse cardiovascular events (O'Neal *et al*., 2015). This risk is highest for those with exercise-induced hypotension. It has also been reported that males and females, whilst utilising the same pathways for stress response, appear to do so with a variation in results (Huang *et al*., 2013), with males showing increased diastolic pressure and total peripheral resistance, whilst females respond by greater changes in heart rate.

6.3.7 Heart Rate Monitoring

Heart rate straps were fitted around each participants' chest (Polar T31 coded strap), connected to a wrist-worn monitor (Polar FT1, Polar Electro Oy, Finland). Heart rate

was measured immediately at the end of each 10-minute bout of exercise, and at the corresponding time point during the control condition. Peak heart rate was determined as the highest visual reading recorded at the completion of each bout.

6.3.7 Statistical Analysis

Data (*n*=11 due to one withdrawal post-randomisation) were analysed using SAS (v. 9.4, SAS Institute Inc, Cary, NC, USA). Subsequent to blood pressure and heart rate, mean arterial pressure (calculated as (SBP+2*DBP)/3), pulse pressure change (the change in the difference between systolic and diastolic blood pressure) and rate pressure product (the product of heart rate multiplied by blood pressure, Gobel *et al*., 1978) were also calculated and analysed. Additionally, residual error, or measurement error, was calculated, with its associated 90% confidence intervals. A linear mixed model, allowing for sex differences in the mean effect of acute exercise and differential period effects between conditions (by sex) was developed, elaborating substantially upon the following 'possible' code previously suggested (Senn *et al*., 2011):

```
proc mixed data=updrs
        class period treat subject;
        me=model score=period treat/ddfm=kr solution CL;
        random subject subject*treat/solution;
        lsmeans treat/pdiff cl;
        ods output solution=randomsolutionf=fixed lsmeans=means;
run;
```

However, this 'possible' code does not adequately partition the variance and allow isolation of the true individual differences in response to acute exercise versus control. Therefore, I rewrote this code by including random effects for the participant x treatment interaction (by period) to partition the variance and derive the 'true' SD for individual responses. This approach allowed for portioning by period (visit 1,2,3,4, whether that be application of intervention or control condition), sex (male, female), treatment (EX, CON), and subject (2-12). In parallel with the method applied to the analysis of parallel group randomised controlled trials, dummy variables are required

to allow extra variance whenever a subject experiences a control trial (xVarC) or a treatment (exercise) trial (xVarT). The following code was developed and applied (SBP used as example analysed variable):

```
proc mixed data=mydata covtest cl alpha=0.1
nobound;
class period treatment subject sex;
model SBP_change=period treatment sex treatment*sex treatment*period
treatment*sex*period/ddfm=satterthwaite outp=pred cl alpha=0.1;
random Subject Subject*xVarC Subject*xVarT
Subject*xVarT*Period;
lsmeans Treatment treatment*sex period treatment*period/diff cl
alpha=0.1;
lsmestimate treatment*sex "exercise-control" 1 -1 -1 1/ cl
alpha=0.1;
run;
```

In the above code SBP change is the change in blood pressure from rest to the end of exercise, or the end of the equivalent control period. The fixed effects provide the overall mean effect of acute exercise versus control, and the differences between men and women in this exercise effect, allowing for period effects, differential period effects between conditions, and differences between sexes in any differential period effects by treatment. Differential period effects between conditions might be due, for example, to a different habituation effect for acute exercise compared with just sitting still.

The sum of the xVarC*subject and xVarT*subject random effects provide the 'consistent' individual differences in response to acute exercise. In addition, 'one-time-only' individual response variance quantifies the different individual responses every time a subject experiences an exercise replicate. To explain, if, within-subject, each subject had the same value on each administration of exercise (but different values between subjects), then there would be consistent individual response variance but zero one-time-only individual response variance. What we see typically in replicate crossovers, however, is that each subject has a <u>different</u> value on repeat.

So, for example, for SBP, Subject 2 has a change score of +59 mmHg on the first exercise occasion and +88 mmHg on the second. So, there will be 'consistent' between-subject differences in response plus 'one-time-only' individual response variance each time a subject experiences an exercise replicate. The total individual response variance in a replicate crossover is therefore the sum of these two variances. The square root of this total individual response variance provides the variability expressed as a SD. The confidence interval for the total individual response variance was derived by squaring the standard errors from each of these variances, adding them together, taking the square root, and then using the normal distribution. This 'total' SD_{IR} is interpreted as the *typical difference between subjects in the mean change between a control trial and an exercise trial.* The model also, of course, gives the mean difference in the change in outcome between exercise and control, with its confidence interval.

6.4 Results

6.4.1 Mean Effects

The mean effect of acute exercise (versus control) on systolic blood pressure are presented in Table 7. The mean difference between females and males was +35 (90%CI 9 – 62) mmHg (67 mmHg in women vs. 32 mmHg in men).

The mean effect on diastolic blood pressure was -6 (-1 to 14) mmHg. The average difference between females and males was 13 (-3 to 28) mmHg. Mean arterial pressure increased by 21 mmHg (13-28), with average sex differences of 21 (6-36), whilst pulse pressure difference was 45 (34 to 55) mmHg, with a difference of 25 (4 to 46) mmHg between females and males. The mean effect on rate pressure product was an increase of 12045 (9058 to 15032). The average difference between males and females was 6006 (21 to 11980), whilst the mean effect on heart rate was an increase of 58 (39 to 78) b.min. The average difference between males and females was 5 (-34 to 45) mmHg.

6.4.2 Consistent Inter-Individual Variation in Response

With sex included in the analysis model, the consistent inter-individual variation in response for systolic blood pressure was 16 (± 90% Confidence Limits 21) mmHg. The consistent inter-individual variation in response for diastolic blood pressure was -10 (±15) mmHg, however, this was overwhelmed by the one-time-only inter-individual variation in response. For mean arterial pressure and pulse pressure, consistent inter-individual variation in response was -4 (±13) and -13 (±23) mmHg respectively, however, like diastolic blood pressure, these were overwhelmed by the one-time inter-individual variation in response. Rate pressure product consistent individual responses was calculated to be 5053 (±4235), and the consistent inter-individual variation in response for heart rate was 26 (±29) b.min.

6.4.3 One-Time Inter-Individual Variation in Response

The one-time only inter-individual variation in response for systolic blood pressure was 11 (±90% Confidence Limits 18) mmHg. The one-time only inter-individual variation in response for diastolic blood pressure was 17 (±19) mmHg, while for mean arterial pressure and pulse pressure, it was 12 (±15) and 27 (±29) mmHg, respectively. Rate pressure product one-time variation was calculated to be 1405 (±1495), whilst the one-time inter-individual variation in response for heart rate was 28 (±27) b.min.

Table 7. Mean and inter-individual variations in response (consistent and one-time), presented with 90% Confidence Intervals/Limits.

	Mean Response (90% CI)	Consistent (±90%CL)	One-Time (±90%CL)
SBP (mmHg)	49 (36 to 62)	16 (21)	11 (18)
DBP (mmHg)	-6 (-1 to 14)	-10 (15)	17 (19)
MAP (mmHg)	21 (13 to 28)	-4 (13)	12 (15)
PP (mmHg)	45 (-35 to 55)	-13 (23)	27 (29)
RPP	12045 (9058 to 15032)	5053 (4235)	1405 (1495)
HR (b.min)	58 (39 to 78)	26 (29)	29 (27)

6.4.4 Residual Error

The residual (measurement) errors for systolic and diastolic blood pressure, mean arterial pressure and pulse pressure were 13 (90%CI 9-23), 11 (8-19), 10 (7-18) and 9 (6-21) mmHg, respectively. Residual error for rate pressure product ($b.min^{-1}$. mmHg) was 480 (324-990), and measurement error for heart rate was 6 (4-14) $b.min^{-1}$.

6.5 Discussion

6.5.1 Key Findings

This is the first study of its kind aimed at quantifying the 'true' inter-individual variation in response to acute exercise using this modified code to properly partition the variance in a linear mixed model. The key findings suggest the presence of 'true' inter-individual variation in response to acute exercise. There was a greater mean blood pressure and heart rate response in females compared to males, larger than might be expected mechanistically, yet different from those reported in Chapter 5. Given the small number of participants, the analysis cannot be stratified by sex, but it appears that there may be substantial sex differences in the acute response to exercise. This should be further investigated by the employment of a large, definitive, trial. Without sex in the analysis model, the total SD_{IR} is 25 mmHg, made up of a consistent SD_{IR} of 23 mmHg and a one-time-only SD_{IR} of 11 mmHg. When sex and sex*treatment and sex*period*treatment are included in the model, the total SD_{IR} goes down to 19 mmHg. This indicates that differential acute responses by sex explain 42% of the total individual response variance. These findings are also different from those presented in Chapter 5, as the same phenomenon is clearly not responsible for the results. Whilst sex does explain some of the observed individual response variance, a substantial amount remains even after accounting for sex. Therefore, these results imply substantial individual response variance in both men and women.

6.5.2 Cardiovascular Reactivity

The association between either systolic (SBP) or diastolic blood pressure (DBP) and the risk of cardiovascular disease (CVD) is well established (JNC, 1997). 'Normal' responses of a rise of 8-12 (ACSM, 2012), 10 (Fletcher *et al*., 2013) or 20 mmHg (Le *et al*., 2008) in SBP per metabolic equivalent have been suggested. Research claims that an exaggerated SBP response, where an increase to more than 180 mmHg is observed, or DBP of more than 95 mmHg during moderate submaximal exercise has been suggested to be the best predictor of new-onset hypertension at 20-year follow up (Yzaguirre *et al*., 2017). However, given that most investigations examining blood pressure response are derived from middle-aged, white males, it is questionable how generalisable these predictors may be. It has been suggested that excessive blood pressure increase during the early stages of graded exercise may actually be more relevant (Currie *et al*., 2018). These authors also suggest the modulating effects of age, sex, fitness, health status and medications should be considered as the observed response may be influenced by any combination of these.

Conversely, reduced cardiovascular reactivity has also been reported to place individuals at increased risk of diseases such as obesity (Carroll *et al*., 2008). In this study, mean changes of 49 mmHg were observed, with the highest observed values of SBP and DBP being 195 and 120 mmHg, respectively. This mean change falls 2 mmHg short of the most accurate discriminator reported for relative maximal exercise induced changes in SBP during exercise to predict incident hypertension (Jae *et al*., 2015), indicating that the highest observed change in this study did not meet thresholds for increased future risk. However, considerable variation between males and females was observed, with females, on average, 35 and 13 mmHg higher, for SBP and DBP, respectively. Whilst mean values were observed to be greater than those previously reported as predictors of cardiovascular-related health, consistent inter-individual variation in systolic blood pressure response of 16 mmHg and heart rate of 26 $b.min^{-1}$ is large in comparison to the mean change. Consistent inter-individual variation in diastolic blood pressure (-10 mmHg), mean arterial pressure (-4 mmHg) and pulse pressure (-13 mmHg) was overwhelmed by the one-time inter-individual variation in response. One-time inter-individual variation in response was also substantial in all variables. However, it is the total individual responses SD that is key. For example,

the overall effect for SBP was 49 ±19 mmHg; this means that a randomly selected subject in this study would be expected to increase SBP by 49 ±19 mmHg in response to a bout of acute exercise of this duration and intensity.

6.5.3 Mechanisms of Response

These data highlight 'true' inter-individual response that is substantial when compared to the mean, greater than might be expected mechanistically. Whilst it is beyond the scope of this chapter to identify the causes, a number of suggestions may shed light on these data. Whilst it is possible that baseline fitness may have been responsible for the observed phenomenon, as a range of fitness levels (22.6-48.2 $mL.kg^{-1}.min^{-1}$) were observed at baseline, it is unlikely that this explains all of the observed variation. There is, however, a clear trend that sex has an impact upon these data, as all variables show greater mean changes in females than males. Whilst baseline testing allowed for estimation of a workload equivalent to 70% of that elicited at $\dot{V}O_2peak$, this workload may have actually been relatively more difficult for females than males. For some individuals, this may have fallen above maximal lactate steady state (MLSS), whilst for others, it may have been below this intensity. Similar findings have been reported with different markers of exercise stress at the same relative workload between trained and untrained individuals (Baldwin *et al*., 2000). Alternatively, these results may be due to the fact that males and females, whilst utilising the same pathways for stress response, appear to differ in response (Huang *et al*., 2013), whereby males often present larger diastolic blood pressure responses to acute exercise. This may uphold the suggestion that male responses are 'vascular' while female responses are 'cardiac' (Allen *et al*., 1993). It is not yet possible to confirm whether the apparent sex difference in intervention effect is due to sex, per se, or to differences in baseline fitness. Very large samples would be required to define multiple intervention interactions with adequate precision.

Given the detrimental role of different causes of stressors, a variety of interventions for the management of stress have been proposed (Hamer *et al*., 2006). Chronic exercise is at the forefront of this approach, as it is proposed to reduce the sympathetic stress response (Crews & Landers, 1987). It can likely attenuate cardiovascular responses to stress, control physiological stress reactivity (Hamer *et*

al., 2006) and may facilitate reduction in cardiovascular disease, stroke and myocardial infarction risk factors (Huang *et al*., 2013). It has been proposed that, whilst little research has been carried out on the acute effects on blood pressure reactivity, acute exercise attenuates stress related blood pressure responses, and repeated exposure to acute bouts may have a positive cumulative effect on cardiovascular responses (Hamer *et al*., 2006). Additionally, each standard deviation reduction in stress-related BP reactivity is associated with a reduction of carotid artery thickness, which may confer positive benefits on acute myocardial infarction risk (Salonen & Salonen, 1993).

6.5.4 Statistical Model for Analysis of Replicate Crossover Data

As previously described, the parallel group RCT is best for evaluating treatment heterogeneity in chronic adaptations. By successfully partitioning the 'consistent' and 'one-time' inter-individual variation in response to exercise, this study has confirmed that the replicate crossover is ideally suited to quantifying the inter-individual variation in acute responses that wash out fully between conditions.

The model used for analysis of these data provides 'consistent' individual responses (from the xVarC*subject and xVarT*subject) and 'one-time-only' individual responses (xVarT*subject*period), which are both random effects. One-time-only individual response variance quantifies the different individual responses each time a subject experiences an EX replicate.

The aforementioned one-time-only individual response variance represents extra physiological variability plus technical error of measurement in the exercise condition at that location. In noisy settings (e.g. difficult data collection) the one-time-only response variance can swamp the consistent individual responses such that the latter cannot be estimated robustly. In this study, as expected, there was more noise in the exercise condition, because of variability of the subject from one bout of exercise to the next and/or because there is more error in the exercise condition – a combination of biological variability and technical error. This is highlighted in the measures (diastolic blood pressure, mean arterial pressure and pulse pressure) where consistent inter-individual variation in response were overwhelmed by the one-time

when using the statistical model, due to the inherent measurement error in relation to the observed change when collecting blood pressure data in exercise studies. This is likely due to the relatively small observed changes in these measures, but future studies may look to replicate this with different blood pressure monitoring techniques, such as continuous blood pressure monitoring.

Whilst SAS analysis code has previously been forwarded to try to partition variance, the elaboration of 'possible' code suggested by Senn *et al*., (2015) presented in this chapter provides a robust, accurate model for the partitioning of variance and the quantification of 'true' inter-individual variation in response to acute exercise interventions.

6.5.5 Limitations

A number of strengths and limitations are evident upon completion of this study. Limitations could be identified through the measurement method for blood pressure within this study. Blood pressure is a notoriously noisy measure, and the blood pressure monitor used was prone to produce occasional error readings. Whilst this was piloted prior to the study, technical issues may still have contributed to the observed variation presented within these data. Most variables had wide confidence intervals/limits due to small participant numbers. However, as a proof of concept, by partitioning the 'consistent' and 'one-time' individual variation, these data show the code produced for the statistical modelling is robust and holds great promise for the future application in larger scale replicate crossovers. In addition to overall N being small (just 11 analysed), the sample contained both men and women, with very few women. Therefore, sex by treatment interactions are purely exploratory and confidence are wide. Wider recruitment for future studies aimed at developing these results would better enable replication efforts and generalisation of the physiological aspect of these data to the wider population. Whilst this study was limited by a small sample, given the observed variability in responses, it is likely that the intensity was sufficient to elicit a range of responses, but as previously stated, may have been relatively more difficult for some than others. Therefore, identification of an exercise intensity that ensured that all participants underwent the same relative intensity may be more appropriate. Quantifying the SD for individual responses with adequate

precision requires large sample sizes, often many time larger than those required for defining mean effects precisely.

6.6 Conclusions

This is the first study of its kind aimed at using this modified code to properly partition the variance in order to quantify the 'true' inter-individual variation in response to acute exercise. While the parallel group RCT is best for evaluating treatment heterogeneity in chronic adaptations, the replicate crossover is ideally suited to acute responses that wash out fully between conditions. The key findings suggest the presence of substantial inter-individual variation in response. The results also highlight the success of the approach in partitioning the different components of variation. Whilst we cannot stratify the analysis by sex, because the numbers are too small, it appears that there may be substantial sex differences in the effect of the acute exercise. To confirm this, a subsequent large definitive trial should be employed, recruited from a wider population, with a focus on blood pressure outcomes utilizing the same analysis procedures.

Chapter 7: Discussion

7.1 Introduction

The main aim of this PhD has been to investigate the appropriate quantification of inter-individual differences in the response to exercise interventions, as well as the exploration of putative moderators and mediators of both the mean intervention effect and the individual response, where appropriate.

7.2 Brief Overview of Literature

The current research sits within the context of repeated reports of marked heterogeneity in the effects of regular exercise training (Hecksteden *et al*., 2018), with inter-individual variability in various phenotypes, such as less than expected weight loss for some individuals, or ranges of $\dot{V}O_2$max response of no change to 40% improvement (Lortie *et al*., 1984, Bouchard & Rankinen, 2001). Nevertheless, recently concerns were raised in regard to the methodological approach of much of the previous body of research (Hopkins, 2015, Atkinson & Batterham, 2015, Williamson *et al*., 2017). The bulk of the literature reports these findings in the absence of a true control sample, often comparing within-group data, or comparing to a spurious statistic such as technical error (TE). The description of variability in response to chronic exercise interventions should only come following comparison with a suitable comparator sample, preferably within a randomised trial design, and comparison of the standard deviation of the change score (SD_{change}) for each group.

Further investigation of possible moderators and/or mediators that may be responsible for 'true' inter-individual response variance should come only after these inter-individual differences in response have been quantified properly (Atkinson & Batterham, 2015, Williamson *et al*., 2017); an approach that has been lacking in the majority of the literature.

7.3 Primary Findings

The primary findings from this programme of work are that, when quantified appropriately, chronic exercise interventions appear to elicit limited 'true' inter-individual variation in response in peak oxygen uptake and weight loss. However, there appear to substantial inter-individual variations in blood pressure and heart rate responses to acute, high intensity 'aerobic' bouts of exercise. Additionally, there appear to be substantial individual responses for chronic blood pressure adaptation in men. Furthermore, substantial individual responses for weight loss with multifactorial interventions in both men and women have been identified. It is particularly important to highlight these findings, as they are vastly differing findings to those presented in Chapter 4, where there is a relative lack of individual response variance for weight loss in response to exercise training alone.

7.4 Thesis Objectives

7.4.1 Thesis Objective 1

The first objective was to critically review the literature on inter-individual variation in maximal aerobic capacity response to exercise. Whilst there have long been claims of inter-individual response to exercise (Prud'homme *et al*., 1984, Despres *et al*., 1984, Lortie *et al*., 1984, Savard *et al*., 1985, Hamel *et al*., 1986, Simoneau *et al*., 1986), it was found that the vast majority of previous investigations of inter-individual differences in $\dot{V}O_2max$ response to exercise training has been conducted almost exclusively without a control group or comparator arm. However, it is the case that the observed variation must be appropriately quantified prior to deeper investigation. This evaluation requires a number of approaches, including the determination of a threshold for meaningful magnitude of change, to establish the presence of clinically important differences in response (Buford *et al*., 2013). In order to quantify the inter-individual response to an exercise intervention, studies should contain the presence of a comparator arm, preferably as an RCT design. This methodological approach is vital, in order to understand the counterfactual, giving our best 'best guess' as to what would have happened to the intervention subjects, had they been, 'contrary to the fact', in the control condition. Furthermore, the

correct statistical analysis and modelling must be used in order to identify the presence of true, clinically relevant, individual response, as unless true inter-individual response exists, it is futile looking for treatment interactions (Senn, 2004). Only when these effects have been properly quantified, using the following equation: $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$, where IR = individual responses, I = intervention or treatment group, and C = control or comparator group (Hopkins, 2015) can the design of experiments to further elucidate the mechanisms responsible for the individual response be confirmed. Indeed, when this approach is taken with data from published research claiming inter-individual variability in response (Prud'homme *et al*., 1984), it was actually observed that there was greater variability in the control sample vs the intervention sample (control ± 5.6 $mL.kg^{-1}.min^{-1}$, intervention ± 3.7 $mL.kg^{-1}.min^{-1}$).

It may also be prudent to measure a number of variables and health outcomes. It may be the case that some participants may improve across some but not all physiological measures, but this approach should be tied to robust hypotheses.

7.4.2 Thesis Objective 2

The second objective of this thesis was to undertake a systematic review and meta-analysis of the weight change literature, with a focus upon quantifying the inter-individual variation in weight loss in response to exercise training. This was the first systematic review and meta-analysis designed and published to address individual variation in response.

The primary findings indicate that evidence is limited for clinically relevant 'true' inter-individual variation in weight change in response to an exercise intervention, once the random variability in weight over time in the control group is accounted for.

When the pooled inter-individual response variability (0.8 kg) is doubled (1.6 kg), as we must for comparison of individual responses, is compared to the pooled mean change in weight (1.4 kg), it is evident that effect sizes are trivial, indicating that there are minimal 'true' inter-individual variation in response to exercise.

A novel concept in meta-analyses is the use of the prediction interval, to quantify the expected range of true effects in future studies in similar settings. The prediction interval for the mean change in weight revealed that, were investigators to undertake a future trial, the 95% plausible range for mean weight change vs. control would be -5.0 to 2.1 kg ('possibly' clinically important; probability 26%). For the individual response variability, the prediction interval ranged from small negative (more response variability in control group) to small positive (more variability in the exercise arm), revealing that the true individual response variability in a future study in similar settings is unlikely to be clinically important (23% chance).

To date, in a manner consistent with the bulk of the literature investigating peak oxygen uptake, much of the research reporting substantial inter-individual differences in response to an exercise intervention has been conducted in the absence of a suitable comparator sample (King *et al*., 2008, Cauldwell *et al*., 2009, Cauldwell *et al*., 2013). As discussed, in order to quantify the true inter-individual response to an exercise intervention, studies should include a comparator arm, preferably in a randomised controlled trial.

7.4.3 Thesis Objective 3

The third objective of the thesis was to conduct a rigorous and detailed secondary data analysis of previously published data set from the PREMIER trial. This analysis showed much larger inter-individual variations in the response of weight loss and blood pressure control (to established treatment and established treatment plus DASH diet) in men, when compared to women, of a magnitude of 3-4 times the MCID. Stratified analyses by sex were undertaken further to the observation of a specious individual response variance for SBP and weight loss from the full model, which was not even partially accounted for by including a sex-by-treatment interaction term in the model. An attenuation of the individual response variance was expected, given the possibly substantial differences in mean treatment effect in men vs. women revealed by the full model. The fact that no such attenuation was observed is a warning sign that the model is mis specified. The paradoxical finding was due to the marked sex differences in individual response variance. The observed

effect in women is relatively consistent, whilst in men it is much more variable. This finding leads to the conclusion that the initially calculated individual response variance for SBP (11.99 mmHg) estimated from the whole sample applies poorly to both men and women, as it underestimates in men and overestimates in women.

The above paradoxical finding reinforces the critical importance of thorough exploratory data analysis before undertaking the primary analysis. I propose that separate analyses by sex should be conducted routinely, to reveal such phenomena. In the PREMIER data set, the large differences in response variance between sexes both overwhelms and offsets any reduction in the observed 'pooled' individual response variance when the sex-by-treatment interaction is included in the model. This finding gives the false impression that sex is not a moderator of individual response variance.

To reiterate, given these observations, researchers and practitioners should therefore be aware that when conducting this type of analysis, care must be taken to investigate and present 'true' inter-individual variation in response by sex, rather than pooling the overall sample, due to the possibility that this phenomenon may be applicable to further datasets.

7.4.4 Thesis Objective 4

The fourth, and final, objective of the thesis was to design and undertake a pilot/ 'proof-of-concept' investigation to investigate the acute inter-individual variation of blood pressure and heart rate variables in response to high-intensity aerobic interval training, using a replicate crossover design. This was the first study of its kind aimed at quantifying the 'true' inter-individual variation in response to acute exercise. This objective was achieved by properly partitioning components of variance using a linear mixed model. The key findings suggest the presence of substantial 'true' inter-individual variation in response. Although there were large sex differences in mean response, with greater blood pressure and heart rate response variables in females in comparison to males, stratified analyses of individual responses by sex were not possible, due to the small number of each in this proof-of-concept trial. In a replicate crossover trial, the total individual response variability is composed of consistent and

one-time-only individual responses. For diastolic blood pressure, mean arterial pressure, and pulse pressure the consistent individual response variance was overwhelmed by the one-time inter-individual variation in response. One-time inter-individual variation in response was also substantial in all variables and consistent inter-individual variation in systolic blood response and heart rate response was large when compared to the mean change. Caution must be used during trial design, as this approach should only be utilised when measuring continuous outcome variables

The large difference in mean response between men and women may indicate that whilst baseline testing allowed for identification of a workload equivalent to 70% of that elicited at $\dot{V}O_2$peak, this workload may have actually been relatively more difficult for females than males. Speculatively, these data may uphold the suggestion that male responses are 'vascular' while female responses are 'cardiac' (Allen *et al*., 1993).

7.5 Methodology in Relation to Current Research

The findings of this programme of work clearly suggested that many of the inferences drawn from previous research might be suspect. Reporting the presence of inter-individual variation in response from an intervention-only trial – or ignoring the control data - clearly lacks the comparator sample with which to compare SD_{change}. This vital component allows us to assess the presence of 'true' inter-individual variation in response.

Whilst it has been argued recently that repeat testing of outcome measures throughout the duration of the intervention can help account for within-subject variability by comparing segmental slopes of change scores for shorter durations across the treatment period (Hecksteden *et al*., 2018), this approach is also limited. Primarily, the close temporal proximity of the measures may lead to high amounts of autocorrelation and a violation of the assumption of random errors. Additionally, it is not clear if training adaptions are linear over the course of an intervention. Also, repeated measures may be both expensive and impractical for some interventions.

Whilst "possible" analysis code for SAS® software has previously been forwarded to try to partition variance in a replicate crossover trial (Senn *et al*., 2015), it must be acknowledged that this code does not properly partition the response variance in intervention and control conditions, and therefore does not quantify individual response variance appropriately.

The analysis code developed and presented in this thesis now permits the proper partitioning of response variance to isolate 'true' inter-individual variation in response to acute interventions, and also has the flexibility to account for sex and period effects. The model separates 'consistent' individual responses and 'one-time-only' individual responses, which quantifies the different individual responses each time a subject experience a treatment (exercise) replicate. This one-time-only individual response variance represents extra physiological variability plus technical error of measurement in the exercise condition at that location. In noisy settings (e.g. difficult data collection) the one-time-only response variance can swamp the consistent individual responses to such an extent that consistent individual responses cannot be robustly quantified. To reiterate, the total individual response variance in a replicate crossover is the sum of these two variances, and the square root is then taken to get the response variability as an SD, as has been previously described (Atkinson & Batterham, 2015).

7.6 Findings in Relation to Literature

The key findings from this thesis indicate that in response to chronic exercise, evidence is limited for the presence of substantial 'true' inter-individual variation in response for peak oxygen uptake and weight loss. This observation is due to the fact that natural random variability over time is similar for intervention and comparator samples, and that little or no extra variance is observed in intervention groups. As previously described, this finding highlights the requirement for a comparator (counterfactual) sample, in order to make firm inferences.

Although it has been suggested that training studies consistently report a high variability in the effects of regular exercise training (Hecksteden *et al*., 2018), and large inter-individual differences in the trainability of the cardiorespiratory system have been claimed for over 30 years (Lortie *et al*., 1984, Bouchard, 1995, Feitosa *et*

al., 2002), re-analysis of the data upon which the majority of these inference are made reveal no clinically important differences in the SD of the change scores between the groups (control ± 5.6 $mL.kg^{-1}.min^{-1}$, intervention ± 3.7 $mL.kg^{-1}.min^{-1}$), (Williamson *et al*.,. 2017). This observation indicates that there are no substantial inter-individual differences in response to the intervention. In fact, these SDs indicate more than double the response variance in the control group versus the intervention group. Such a phenomenon can result when an intervention has a harmonising effect on the outcome variable in question.

Despite claims of inter-individual variation in fat loss and weight loss in response to exercise that were previously reported (Snyder *et al*., 1997, Byrne *et al*., 2006, King *et al*., 2008, Caudwell *et al*., 2009, Church *et al*., 2009, Barwell *et al*., 2009), which result in a prevailing opinion that exercise often results in less than expected weight loss (Donnelly & Smith, 2005), the findings of this PhD study indicate that this is not the case. Mean weight loss of 1.4 (95% CI -0.3 to -2.5) kg, and 'true' inter-individual variation in response of 0.8 (-0.9 to 1.4) kg indicate that any observed inter-individual variation in response does not even meet a conservative minimally important difference threshold.

7.7 Recommendations to Policy Makers and Practitioners

Precision medicine might improve population health, given that we may require both individual and public health approaches to improve health. Population health planning requires directing efficient use of resources toward those most at risk. Past successes of genomics and precision medicine indicate that they can yield population health benefit.

However, precision interventions may not improve population health due to the nature and complexity of disease pathogenesis, particularly for common chronic diseases. Therefore, the promise of precision medicine to identify predictors of disease that can help guide personalized interventions may not be easily fulfilled. Additionally, the precision medicine agenda could shift resources from other areas, and its appeal may lead to hype and premature expectations that may cause long-term disillusionment and erosion of public confidence in health sciences.

A major challenge ahead is figuring out how to best use the available large-scale data ranging from genomic to environmental information sources. These data should only be utilised if they will help us better understand determinants of population health and interventions that will improve health outcomes in subpopulations. Given the findings presented here, it is highly likely that for many phenotypes, interventions that work 'on average', targeted to whole populations (i.e. the mean response) will suffice until further evidence accumulates (Harrell, 2018), as the evidence for substantial chronic inter-individual response variation is limited.

Whilst wide scale DNA collection and analysis has been proposed for identifying inter-individual variations, even the large scale and well-funded All of Us programme in the United States has struggled. Despite $1.5bn in funding over ten years, in its first three years, not a single set of DNA has been sequenced. This further highlights the problem surrounding this approach. Due to its complexity, is this funding the best use of resources? Should the funding instead go to research conducting truly applied and innovative science?

Therefore, for the vast majority of outcomes, the idea that a personalised approach is necessary seems questionable. It also seems unlikely that, given the complexity of the biological and social contributors to weight loss, increased physical activity etc., that small lifestyle tweaks based upon information regarding very small numbers of genes will provide a benefit over and above those elicited from following general lifestyle guidance. There is also little evidence that the provision of information regarding inter-individual variation in response, or genetic risk information, will actually motivate the individual to undertake behaviour change. Given these facts, it may be more prudent to use alternative approaches, such as risk magnification, which has been described as providing the largest absolute risk reduction (Harrell, 2018) This approach uses statistical tools and standard clinical variables to improve medical and public health decision making, therefore cutting costs in comparison to precision medicine.

Genetics-informed approaches and precision medicine have gained a toehold in the consciousness of exercise professionals, medical researchers, and large-scale funders

in recent years, built upon the principle of health care revolution. This increase in awareness has been necessary for scientists and research institutions to obtain research funding from public and private organisations but, as yet, there is little beyond unproven hype. Whilst continuing research may be worthwhile, focus should be directed upon evidence-based basic scientific principles of mechanistic adaptation, rather than genetic testing for risk profiling, athlete development, and predictions of response by body type.

Ultimately, precision interventions to target those who may display inter-individual variations in response are just a small tool in the box. Whilst with further research it may facilitate better outcomes, without the correct quantification methods to inform research and practice, ultimately it may cause more harm than benefit. Therefore, for chronic exercise interventions, practitioners should utilise the RCT approach, in combination with the analysis of SD_{change} of the intervention sample vs. the control. Alternatively, to identify the presence of inter-individual variation in response to acute bouts of exercise, the replicate crossover approach, using the code and analysis presented herein to fully partition the observed variance. It is also vital that practitioners ensure selection of valid, reliable measurement tools and high levels of inter- and intra-rater reliability in order to minimise measurement error in exercise trials.

There have yet to be any examples of true precision interventions with successful outcomes. Population-wide approaches focusing on physical and social environments should also be considered. Clearly, policy makers and practitioners should understand the value of high-quality research, and inferences drawn from such; care should be taken when practical recommendations are suggested from research not utilising the methodology and statistical analysis recently suggested (Hopkins, 2015, Atkinson & Batterham, 2015, Williamson *et al*., 2017, Williamson *et al*., 2018).

7.8 Strengths of the Thesis

A number of strengths are clear in this current body of research. In Chapter 4, I presented the first systematic review and meta-analysis of individual response

variance. In order to make inferences from the data extracted and analysed in this meta-analysis, I adopted a threshold for the minimum clinically important weight loss of 2.5 kg – the smallest threshold of absolute weight loss for clinical benefit previously reported (Jensen *et al*., 2014). This was a very conservative estimate of an MCID, and if a less conservative MCID were to be used, the argument against the observation of 'true' inter-individual variation in weight loss would be further strengthened.

The subject matter for the meta-analysis, and the inclusion of the prediction interval, for an indication of what may happen in any future similar trial, are both novel. Additionally, the primary data collection presented in Chapter 6 is a novel approach. This was the first study of its kind designed specifically to investigate the inter-individual variation in response to acute exercise.

Finally, the statistical model used to analyse the data collected in the acute replicate crossover trial was proved to be a robust model, due to its ability to accurately partition variance, and identify both the consistent and the one-time only inter-individual variation in response.

7.9 Limitations of the Thesis

A number of limitations are also evident upon completion of this programme of work. In regard to the meta-analysis presented in Chapter 4, the energy expenditure induced by the exercise interventions undertaken in the included studies – and whether this would be sufficient, in theory, to induce weight loss above the minimal clinically important difference – is unknown. It is therefore unknown what effects exercise protocols with larger energy expenditures would elicit. The literature search was restricted to RCTs incorporating exercise-only interventions; included studies that differed by exercise mode, intensity, frequency and duration, and length of intervention. This intervention heterogeneity may have influenced mean effects and/ or individual response variance. However, there were too few studies to compare the effects in different intervention types.

In relation to the acute exercise trial, most effects had wide confidence intervals/limits due to small participant numbers. However, as a proof of concept, these data show the code produced for the statistical modelling is robust and holds great promise for the future application in larger-scale replicate crossovers.

Additionally, whilst using the model suggested, a differential period effect between control and exercise conditions was observed, due to a different habituation effect for acute exercise compared with sitting still. This effect is evaluated by adding a treatment x period fixed effect to the model and getting the least-squares means for the interaction.

7.10 Original Contributions to Knowledge

In this thesis I have undertaken a meta-analysis of 1500 participants in exercise intervention studies. The key original contribution to knowledge is that, across 12 studies, while mean weight change was -1.4 kg, the individual response variability (SD) was only 0.8 kg, highlighting very limited evidence for the notion of individual variation of weight change in response to an exercise intervention. This novel analysis utilised, for the first time in this field, a prediction interval for inter-individual variation, which identified that the likelihood of 'true' inter-individual variation in response to an exercise intervention is limited, with only a 23% chance that in a future study in similar settings any observed response variation would be clinically relevant.

These findings have already been published in the high-quality, peer reviewed journal *Obesity Reviews* (Williamson *et al*., 2018). This research has thus provided an original, robust protocol that has provided an important insight into how to quantify inter-individual variation in response to exercise and to implement a prediction interval for future studies in similar settings.

In addition, a further original contribution to knowledge comes through the development of a model with which to partition individual variation in response for acute effects in replicate crossover designs. Using the model with interactions to identify 'consistent' individual responses (xVarT*subject) and 'one-time-only'

individual responses (xVarT*subject*period), provides a robust, accurate model for the partitioning of variance and the quantification of 'true' inter-individual variation in response to acute interventions when measuring continuous outcome variables.

7.11 Future Research Considerations

Whilst it is well documented that long-term systematic resistance training causes increased skeletal muscle size and strength in both men and women of different ages, resistance training-induced gains in muscle size and strength are often claimed to be variable between individuals. Large variability in both muscle size and strength gains in response to resistance training between individuals has been previously reported (McGlory & Phillips, 2015). In a large study, men and women were reported to exhibit wide ranges of strength gain (1 RM: 0 to +250%) and skeletal muscle hypertrophy (cross-sectional area: -2 to +59%) in response to 12 weeks of resistance training (Hubal *et al*., 2005), indicating individual training responses may vary widely dependent on factors such as genetic heritage. Whilst approximately 6% showed practically no gains in muscle size, no control group was utilised in this study, so it is difficult to interpret the results presented without the availability of a suitable comparator.

Other resistance training studies have reported that, in some subjects, muscle size gains are either minimal or non-existent following a training intervention (Bamman *et al*., 2007, Davidsen *et al*., 2011, Raue *et al*., 2012, Mitchell *et al*., 2013, Phillips *et al*., 2013). Similarly to muscle size responses, gains in muscle strength during resistance training are also highly individual (Hubal *et al*., 2005; Erskine *et al*., 2010). However, the range of individual responses to resistance training in people of different ages has not yet been elucidated. This question is particularly relevant considering how people respond to a resistance-training programme based on physical activity recommendations for health. In each of these studies, the recurring theme of no comparator group is evident. These are interesting findings and highlight that further study is warranted in this domain.

Given the findings of the proof-of-concept study reported in Chapter 6, in order to replicate these findings, it is of prime importance to develop this methodology, and undertake a similar trial on a larger scale, focusing on blood pressure outcomes and

utilizing the same analysis procedures. These findings, if replicated through a large-scale research study, may have important implications on practice and policy for clarification of inter-individual variation of blood pressure reactivity in response to an acute bout of exercise. Furthermore, if these findings are replicated, detailed investigation of possible moderators and mediators for the reported findings will be warranted. Therefore, further research should be focused upon the elucidation of these contributing factors to any observed inter-individual variation.

Future work should employ the research designs suggested in this thesis, incorporating sound statistical quantification of the response variance in each arm, combined with a threshold for the minimal clinically important difference, to determine the presence of clinically important individual variation in response. Whether these future studies observe the presence of 'true' inter-individual variation in response or not, this should be disseminated through peer-reviewed publications, in order to add to the body of literature pertaining to this current hot topic.

7.12 Summary of Evidence

In summary, the studies undertaken in this research project have highlighted the consistent lack of a comparator sample within previous research purporting to show inter-individual variation in response. When re-analysis of rare control sample data presented by these authors is undertaken, more variation is observed in the control group in comparison with the intervention group. The systematic review and meta-analysis revealed that when studies containing a comparator sample within an RCT design are meta-analysed, there is limited evidence for substantial inter-individual variation in weight loss response to exercise training. Furthermore, when previous data from a large-scale lifestyle change trial is re-analysed, whilst individual response is apparent, further scrutiny of the initial findings reveal that the observed individual response is inaccurate for both men and women. Further analyses stratified by sex are required, revealing substantial inter-individual variation in blood pressure response in men, compared to women.

Finally, in response to acute exercise, a newly-designed analysis model for replicate crossover studies with continuous outcome variables allows for the accurate partitioning of ‘one-time’ and ‘consistent’ inter-individual variation in response. This analysis reveals the presence of ‘true’ inter-individual variation in response.

Appendices

Appendix 1 – Participant Information Sheet

Participant Information Sheet

Research title: Individual differences in the acute physiological responses to intermittent exercise: A replicated crossover study

I, Phil Williamson, am a PhD student in the School of Health and Social Care. I would like to invite you to take part in our research study. Prior to deciding to participate, please read the following information and discuss it with others if you wish. Please ask me if you have any questions.

What is the purpose of the study?

The study aims to quantify clinically-relevant inter-individual differences in blood pressure responses to sub-maximal intermittent exercise.

Who is responsible for the study?

The researchers are Philip Williamson (PhD student, HSCI), Prof Alan Batterham (Supervisor, HSCI) and Prof Greg Atkinson (Supervisor, HSCI).

Why have I been invited to take part?

You have been invited because you are a student at Teesside University, and I wondered if you may be interested in taking part. To participate in the present study, you must be healthy and aged 18 or older. Importantly, you are not eligible if you:

- have any diagnosis or symptoms of cardiovascular or metabolic diseases (e.g. heart disease, diabetes)
- present an injury requiring alterations of the established exercise protocol
- are physically unable to complete the intervention
- have been advised by a health professional to avoid physical exercise or activity
- are taking any medication
- are pregnant or
- do not have a satisfactory score on the attached PARQ+. Please read through this yourself to see if you are eligible and your score will be re-checked at your first attendance if you want to take part

Please, feel free to show a copy of this invitation to anyone else who may wish to take part. Anyone who meets the eligibility criteria is most welcome to express an interest in participating.

Do I have to take part?

No. It is your personal choice whether or not you decide to participate. You are also free to withdraw the study at any time if you want to up to the point of completing your final data collection session in the laboratory. If at any point you wish to withdraw from the study, we ask that you contact Prof Alan Batterham, the Director of Studies, in the first instance (A.Batterham@tees.a.c.uk). As data will be anonymised, it is requested that you keep your individual participant information sheet upon enrolment, as this will be used to retrieve and remove any coded data pertaining to your involvement, should you wish to withdraw at any time.

What will happen to me if I take part?

You will be invited to attend laboratory sessions on five occasions taking place in the Exercise Physiology Laboratory in the Olympia Building/Constantine Building at Teesside University. To avoid alcohol (24h) and caffeine (12h) consumption, and strenuous exercise (24h) prior each visit is required. At the first session, we will check your responses on the attached PARQ+ to ensure that you may take part.

At the first session, you will be given a physical activity questionnaire to complete. Once it has been confirmed that there are no medical conditions precluding your participation in the research project, an informed consent form to be completed. On the same occasion, you'll be asked to complete a familiarisation session, and demographic information involving your height, weight, gender, age, and resting blood pressure will be recorded. Peak oxygen uptake shall then be assessed on a cycle ergometer. Subsequently, you'll be assigned to each of the two experimental conditions of sub-maximal and no exercise to be completed in a random order. Each visit is characterised by two phases. Firstly, your blood pressure will be measured during a 30-min supine resting. Secondly, in the exercise condition, you'll perform three 10-min cycling at 70% of your peak oxygen uptake interspersed with 5-min recovery periods. Measurements of your blood pressure will be repeated during each resting interval. Similarly, we'll adopt the same procedures regarding blood pressure

measurements when you are assigned to the control condition, but you'll remain sat on the cycle ergometer without undertaking any physical exercise. As mentioned previously, each condition will be repeated twice. Overall, each experimental session should take approximately 90 minutes.

What are the possible disadvantages or advantages of taking part?

There are certain risks to participating, such as discomfort or injury from undertaking intermittent exercise. There are no direct benefits from participating, although $\dot{V}O_2$peak is an established method for appraising cardiorespiratory fitness which may be of interest.

Confidentiality

All the collected information during the study will be kept strictly confidential. None of the measurements will be in the public domain as the data is anonymised. All electronic data will be stored on a password protected Teesside University server. Your non-identifiable data will be kept confidential and stored for up to 20 years at Teesside University and could be used in future studies having obtained the required ethical approval from a designated Research Governance and Ethics Committee.

How will the data be used?

The results of this study will be included in our PhD theses and future scientific articles submitted for publication in peer-reviewed journals and conference presentations. Collected data and results will be anonymous and no identifiable information will be revealed.

What happens if there are any problems?

The methods used in this study have been safely adopted in previous clinical investigations, although the present study is covered by University's insurance policies. If you felt you had been harmed in anyway by taking part in this study you should contact the Associate Dean for Research and Innovation in the School, Prof John Dixon (John.Dixon@tees.ac.uk) in the first instance if you should have any complaints about the study.

Who approved the study?

This project has been reviewed and approved by the School of Health & Social Care Research Governance and Ethics Committee at Teesside University. The Chair of this committee is Dr. Alasdair Macsween.

Who can I contact for more information?

If you have any queries or you would like to receive more information please contact: Philip Williamson at P.Williamson@tees.ac.uk.

Additionally, you can contact Professor Greg Atkinson via e-mail (Greg.Atkinson@tees.ac.uk) albeit not directly involved in booking appointments for data collection.

Thank you for reading this information sheet and for your consideration on taking part in the study.

Appendix 2 – Initial Contact Email

Hello,

My name is Philip Williamson and I am a PhD research student at Teesside. I am writing to ask if you would consider taking part in my research project. I want to investigate the acute inter-individual responses of blood pressure to intermittent exercise and the acute changes in ankle brachial index. The title is, **Individual differences in the acute physiological responses to intermittent exercise: A replicated crossover study.**

I have attached a participant information sheet which explains the study and if you are interested please do read it. Please don't be put off by the words *intermittent* exercise*;* you won't be expected to suffer! I have also attached an initial PARQ to enable me to assess your medical eligibility for inclusion in the study.

I will be sending out two reminder emails about the study - one in two weeks and then again two weeks later. Doing this has been shown to greatly improve recruitment to studies. Please accept my apologies in advance if you have already decided you don't want to take part when you receive those.

If you have any questions and/or would like to express an interest in taking part, then please contact myself on P.Williamson@tees.ac.uk. You can also contact my supervisor Alan Batterham and Greg Atkinson on A.Batterham@tees.ac.uk or Greg.Atkinson@tees.ac.uk

Appendix 3 – Initial Course Lead Contact

Hello,

My name is Philip Williamson and I am a PhD research student at Teesside. I am writing to ask if you would please help me by forwarding the invitation e-mail and Participant Information Sheet (attached) to all your students? I want to investigate the acute inter-individual responses of blood pressure to intermittent exercise and the acute changes in ankle-brachial index. The title is, **Individual differences in the acute physiological responses to intermittent exercise: A replicated crossover study.**

I will be sending out two reminder emails about the study - one in two weeks and then again two weeks later. Doing this has been shown to greatly improve recruitment to studies. If you will not forward our email on to your students and you don't want to receive any reminders, please let me know and I won't send them to you.

Thank you for considering helping us to recruit.

Please don't hesitate to contact me if you have any questions on P.Williamson@tees.ac.uk. You can also contact my supervisor Alan Batterham and Greg Atkinson on A.Batterham@tees.ac.uk or

Appendix 4 – Initial Invite via Subject Lead

Hello,

My name is Philip Williamson and I am a PhD research student at Teesside. Your Subject Lead obtained your contact details from their database and has sent you this on our behalf. I do not know who they have contacted, no information about you, nor your contact details have been given or shown to me. I would like to ask you if you would please consider taking part in my research project? I want to investigate the acute inter-individual responses of blood pressure to intermittent exercise and the acute changes in ankle-brachial index. The title is: **Individual differences in the acute physiological responses to intermittent exercise: A replicated crossover study.**

I have attached a participant information sheet which explains the study and if you are interested please do read it. Please don't be put off by the words *intermittent exercise;* you won't be expected to suffer! I have also attached an initial PARQ to enable me to assess your medical eligibility for inclusion in the study.

I have asked your Subject Lead to send out two reminder emails about the study - one in two weeks and then again two weeks later. Doing this has been shown to greatly improve recruitment to studies. Please accept our apologies in advance if you have already decided you don't want to take part when you receive those.

If you have any questions and/or would like to express an interest in taking part then please contact me if you have any questions on P.Williamson@tees.ac.uk. You can also contact our supervisor Alan Batterham and Greg Atkinson on A.Batterham@tees.ac.uk or Greg.Atkinson@tees.ac.uk

Appendix 5 – Informed Consent

Individual differences in the acute physiological responses to intermittent exercise: A replicated crossover study

Researcher: Phil Williamson

Supervisor: Professor Alan Batterham

Please put your initials in the boxes to indicate your agreement with the corresponding statements.

I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐

I meet the inclusion criteria for participation in the study. ☐

I know that I have the right to withdraw any data collected from me up until the final (third) data collection session is complete. ☐

I agree to my data being stored on a password protected server ☐

I agree to take part in this study ☐

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Name of Participant	**Date**	**Signature**

----------	----------	----------
Name of Witness	**Date**	**Signature**

Appendix 6 – Adverse Event

CONFIDENTIAL

ADVERSE EVENTS FORM

Subject ID:				**Subject Initials:**				**D.O.B**			
Age:				**Gender: M / F**							

Were there any Adverse Events?

(Please check appropriate box)

Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
☐ yes	☐ no	☐ yes	☐ no	☐ yes	☐ no	☐ yes	☐ no	☐ yes	☐ no

If no Adverse Events (AE) were reported, no signature from the PI is required. Any adverse event will be reported to and reviewed by Prof Alan Batterham (Director of Studies) as soon as possible. Where relationship to experimental procedures is scored 2-5, the event will be reported to Marion Grieves and Alasdair MacSween as soon as possible.

Severity	1 = Mild	☐
	2 = Moderate	☐
	3 = Severe	☐
Relationship to experimental procedures	1 = Definitely not related	☐
	2 = Probably not related	☐
	3 = Possibly related	☐
	4 = Probably related	☐

	5 = Definitely related	☐
Action taken	1 = Discontinued from study	☐
	2 = Hospitalized	☐
	3 = None	☐
	4 = Other (Comment)	☐
Outcome at date ceased	1 = Recovered	☐
	2 = Recovered with sequelae	☐
	3 = Died (Comment)	☐
	4 = Other (Comment)	☐

ADVERSE EVENTS FORM

Adverse Event	Date of Onset dd/mm/20□□	Date Ceased dd/mm/20□□	Severity	Action taken	Outcome
	□□/□□	□□/□□			
	□□/□□	□□/□□			
	□□/□□	□□/□□			
	□□/□□	□□/□□			

Signature:

Examiner:

_____

Date:_

_____

_____

_____

PI:

_____

____ Date:_

_____

_____

Appendix 7 – Risk Assessment

This form should be used for all modules (including those delivered in colleges or other sites) which include a practical element (e.g. physical activity, practical/creative skill development, interactive skill development activity e.g. counselling techniques). Risk is determined by cross-referencing the hazard effect and probability on the following chart. Each module leader should ensure that potential risks specific to their module are identified in the 'Potential risk' column and the level of risk assessed. This should include risks to students, staff and equipment. The form should be kept in the module 'box'. This form is in addition to risk assessments carried out in relation to building and environment.

	Hazard Effect		
Probability	**Low**	**Medium**	**High**
Very Low	Trivial Risk	Trivial Risk	Low Risk
Low	Trivial Risk	Low Risk	Medium Risk
Medium	Low Risk	Medium Risk	High Risk
High	Medium Risk	High Risk	Intolerable Risk

Hazard Effect:

Low Superficial wounds or temporary ill health.

Medium More serious wounds and ill health leading to permanent, minor disability.

High Fatality, life threatening wounds and life shortening diseases.

Probability:

Very Low So unlikely that probability is close to zero.

Low Unlikely but conceivable.

Medium Could occur several times.

High Occurs repeatedly and could be expected.

Part One:

Work Area/Job: Student Research study

Location: C1.12, Constantine Research Lab, Teesside University, Olympia Physiology Labs

Study Title: Individual differences in the acute physiological responses to intermittent exercise: A replicated crossover study

Completed by: Philip Williamson

Part Two:

Potential	Hazard Present		Cause of Hazard	Hazard Effect	Probability	Risk
	Yes	No		Low/Med /High	Very Low/Low/ Med/ High	Trivial/Low/ Med/High/ Intolerable
Injury from undertaking intermittent exercise	X		Exercising above habitual levels	Low	Low	Trivial
Injury from measurement of ABI	X		Pressure	Low	Low	Trivial
Cross infection from gas analyser	X		Cross infection	Low	Low	Trivial

Risk Assessment Record

Part Three

Result of Risk Assessment: **Trivial X** Low ☐ Medium ☐

High ☐ Intolerable ☐

Safety procedures implemented (if result is Medium, High or Intolerable).

N/A

Final result of Risk Assessment after safety procedures implemented.

Trivial X

Low ☐

Medium ☐

Appendix 8 – PAR-Q

Name	**DoB**

Male ☐ **Female** ☐

Contact no.	**Email**
Address	

Emergency Contact

Name	**Relationship**
Contact no.	

Medical contact details

Doctor	**Contact no.**

Physical activity readiness questionnaire (PAR-Q)

Questions	**Yes**	**No**
Has your doctor ever said you have a heart condition and can only perform exercise that has been recommended by a doctor?		
Do you feel pain in your chest when you exercise?		
Have you felt any chest pain when you are not exercising within the last month?		
Do you lose your balance due to dizziness or do you lose consciousness?		
Do you have any joint or bone issues that may be made worse due to a change in exercise habits?		
Are you currently being prescribed any medication by your doctor for a blood pressure or heart related condition?		
Do you know of any other reason why you may not participate in exercise?		

Outcome

Medical clearance not necessary	
Medical clearance recommended	
Medical clearance required	

I confirm that I have read the questions fully and answered each question honestly. If there are any changes in my health I will inform the investigators immediately.

Signature	Date

Appendix 9 – Data Collection Sheet

Initials: ID Code: EX/CON: 1/2

Power required (EX ONLY):

Resting BP: Resting HR:

Pre exercise BP (dorsalis pedis): (posterior tibial):

After 1st interval BP (brachial): After 1st interval HR:

After 1st interval RPE:

After 2nd interval BP (brachial): After 2nd interval RPE:

After 2nd interval BP (dorsalis pedis): (posterior tibial):

After 2nd interval HR:

Post exercise BP (brachial): Post exercise HR:

Post exercise BP (dorsalis pedis): (posterior tibial):

Post exercise RPE:

Appendix 10 – Abstract 1 (Conference Abstract)

Inter-Individual Differences in the Responses of $\dot{V}O_2$max to Physical Activity Counselling

Presented at The International Sports Science and Sports Medicine Conference, 2016.

Abstract

Low cardiorespiratory fitness ($\dot{V}O_2$max) is an important risk factor for diabetes, cardiovascular disease and some cancers, making lifestyle interventions especially relevant. There is purported to be substantial inter-individual differences in how $\dot{V}O_2$max responds to lifestyle/exercise interventions. Recently, we described the appropriate approach for quantifying these inter-individual differences. Therefore, we aimed to apply this approach to quantify inter-individual differences in the responses of $\dot{V}O_{2max}$. We re-analysed data from the influential 'Activity Counselling Trial' (ACT), which was designed to determine the effects of general lifestyle assistance as well as formal counselling on physical activity and $\dot{V}O_2$max in 479 men and 395 women. Importantly, an appropriate comparator group was also present in order to quantify 'true' inter-individual differences in $\dot{V}O_2$max response. For women, the 'true' inter-individual responses in $\dot{V}O_2$max (expressed as a SD) were found to be ± 129 (95% Confidence interval: -40 to 187) ml/min in the general lifestyle assistance group and ± 93 (-91 to 160) ml/min in the formal lifestyle counselling group. For men, true individual differences in response were ± 116 (95%CI: -130 to 210) ml/min and ± 148 (-105 to 234) ml/min in the assistance and counselling groups, respectively.

Although the mean increase in $\dot{V}O_2$max was greater in women, this increase corresponded to a trivial effect size. This application of the appropriate analyses to the ACT dataset indicate that, on average, the effects of activity counselling on $\dot{V}O_2$max were small, although there were moderate 'true' inter-individual differences in the $\dot{V}O_2$max response in women (0.34 SD) and small 'true' inter-individual differences in men (0.27 SD). Further genotype investigation may therefore be

warranted in order to determine the mediators of this observed heterogeneity in response.

Appendix 11 - Abstract 2 (Conference Abstract)

Inter-Individual Responses of Maximal Oxygen Uptake to Exercise Training: A Critical Review

Also published in Sports Medicine. 2017;47:1501-13.

Abstract

It has recently been reported how to quantify inter-individual differences in the response to an exercise intervention using the standard deviation of the change scores, as well as how to appraise these differences for clinical relevance. In a parallel-group randomised controlled trial, the key trigger for further investigation into inter-individual responses is when the standard deviation of change in the intervention sample is substantially larger than the same standard deviation derived from a suitable comparator sample. 'True' and clinically relevant inter-individual differences in response can then be plausibly expected, and potential moderators and mediators of the inter-individual differences can be explored. We now aim to critically review the research on the inter-individual differences in response to exercise training, focusing on maximal oxygen uptake ($\dot{V}O_2max$). A literature search through the relevant bibliographic databases resulted in the identification of six relevant studies that were published prior to the influential HEalth, RIsk factors, exercise Training And Genetics (HERITAGE) Family Study. Only one of these studies was found to include a comparator arm. Re-analysis of the data from this study, accounting for random within subjects variation, revealed an absence of clinically important inter-individual differences in the response of $\dot{V}O_2max$ to exercise training. The standard deviation of change was, in fact, larger (±5.6 $mL.kg^{-1}.min^{-1}$) for the comparator than the intervention group (±3.7 $mL.kg^{-1}.min^{-1}$). We located over 180 publications that resulted from the HERITAGE Family Study, but we could not find a comparator arm in any of these studies. Some authors did not explain this absence, while others reasoned that only inter-individual differences in exercise response were of interest, thus the intervention sample was investigated

solely. We also found this absence of a comparator sample in on-going studies. A perceived high test–retest reliability is offered as a justification for the absence of a comparator arm, but the test–retest reliability analysis for the HERITAGE Family Study was over a much shorter term than the length of the actual raining period between baseline and follow-up measurements of $\dot{V}O_2$max. We also scrutinised the studies in which twins have been investigated, resulting in concerns about how genetic influences on the magnitude of general within-subjects variability has been partitioned out (again in the absence of a comparator no-training group), as well as with the intra-class correlation coefficient approach to data analysis. Twin pairs were found to be sometimes heterogeneous for the obviously influential factors of sex, age and fitness, thereby inflating an unadjusted coefficient. We conclude that most studies on inter-individual differences in $\dot{V}O_2$max response to exercise training have no comparator sample. Therefore, true inter-individual differences in response cannot be quantified, l*et al*one appraised for clinical relevance. For those studies with a comparator sample, we found that the inter-individual differences in training response were not larger than random within-subjects variation in $\dot{V}O_2$max over the same time period as the training intervention.

Appendix 12 - Abstract 3

Inter-Individual Differences in Weight Change Following Exercise Interventions: A Systematic Review and Meta-analysis of Randomised Controlled Trials

Published in Obesity Reviews. 2018;19:960-75.

Abstract

Previous reports of substantial inter-individual differences in weight change following an exercise intervention are often based solely on the observed responses in the intervention group. Therefore, we aimed to quantify the magnitude of inter-individual differences in exercise-mediated weight change. We synthesized randomised controlled trials (RCT) of structured, supervised exercise interventions. Fourteen electronic databases were searched for relevant studies published up to March 2017. Search terms focused on structured training, RCTs and body weight. We then sifted these results for those RCTs (*n*=12, 1500 participants) that included relevant comparator group data. Standard deviations (SD) of weight change were extracted, thereby allowing the SD for true inter-individual differences in weight-loss to be calculated for each study. Using a random effects meta-analysis, the pooled SD (95% CI) for true individual responses was 0.8 (-0.9 to 1.4) kg. The 95% prediction interval (based on 2SDs) for true inter-individual responses was -2.8 to 3.6 kg. The probability (% chance) that the true individual response variability would be clinically meaningful (>2.5 kg) in a future study in similar settings was 23% ('unlikely'). Therefore, we conclude that evidence is limited for the notion that there are clinically important individual differences in exercise-mediated weight change.

Appendix 13 - Abstract 4 (Conference Abstract)

Inter-Individual Differences in Acute Blood Pressure Response to High Intensity Exercise: A Replicate Crossover Design

Presented at The European College of Sport Science Congress, 2018.

Introduction

Acute blood pressure responses to physical activity predict hypertension and other cardiovascular-related comorbidities (Atkinson *et al*., 2013). Robust quantification of individual differences in this blood pressure reactivity requires a controlled replicate crossover design to isolate the participant x condition response variance (Senn, 2016; Goltz *et al*., 2017). Our aim was to conduct the first appropriately designed experiment on individual differences in acute blood pressure reactivity to exercise.

Methods

After baseline assessment of peak oxygen uptake, twelve normotensive adults (4 women) with mean (SD) age: 29.7 (4.9) y, height: 173.9 (10.1) cm, body mass: 72.5 (12.5) kg were randomized in blocks of 2 to one of 6 possible sequences of 2 control and 2 exercise replicates over 4 periods. The exercise comprised two 10-min bouts of cycling at 70% of the power output exhibited at peak oxygen uptake, separated by a 5-min recovery period. In the control condition, participants rested on the cycle ergometer for the equivalent time. Blood pressure was measured at rest and immediately after the last exercise bout (or at the end of the control period). Data (n=11 due to one withdrawal post-randomization) were analysed using a linear mixed model, allowing for sex differences in the mean effect of acute exercise and differential period effects between conditions (by sex). We included random effects for the participant x treatment interaction (by period) to partition the variance and derive the true SD for individual responses.

Results

The mean effect of acute exercise (versus control) on systolic blood pressure was an increase of 49 (90% CI, 36 to 62) mmHg (67 mmHg in women vs. 32 mmHg in

men). The consistent SD for individual responses – the typical inter-individual difference between participants in the mean change between a control trial and an exercise trial - was 16 (±90% Confidence Limits - 21) mmHg. The one-time inter-individual variation in response was 11 (±18) mmHg.

Discussion

In the first replicate crossover study quantifying inter-individual variability in response to exercise, we have shown a very large typical difference between participants in the mean effect of acute exercise on systolic blood pressure. We emphasize that although individual response variance was substantial, such a finding does not imply, necessarily, that there are 'responders' and 'non-responders' – in the current study all participants were responders to acute exercise. This model can be applied to future replicate crossover trials to quantify the presence of inter-individual variation in response to acute exercise.

References

Atkinson G, Batterham AM, Kario K, *et al*. Eur J Appl Physiol. *et al*. 2014;114:521-9.

Goltz FR, Thackray AE, King JA, *et al*. Med Sci Sports Exerc. 2018. Ahead of Press. DOI: 10.1249/MSS.0000000000001504

Senn S. Stat Med. 2016;35:966

Appendix 14 – Peer-Reviewed Paper – Inter Individual Responses of Maximal Oxygen Uptake to Exercise Training; A Critical Review

Inter-Individual Responses of Maximal Oxygen Uptake to Exercise Training: A Critical Review

Philip J. Williamson, Greg Atkinson & Alan M. Batterham

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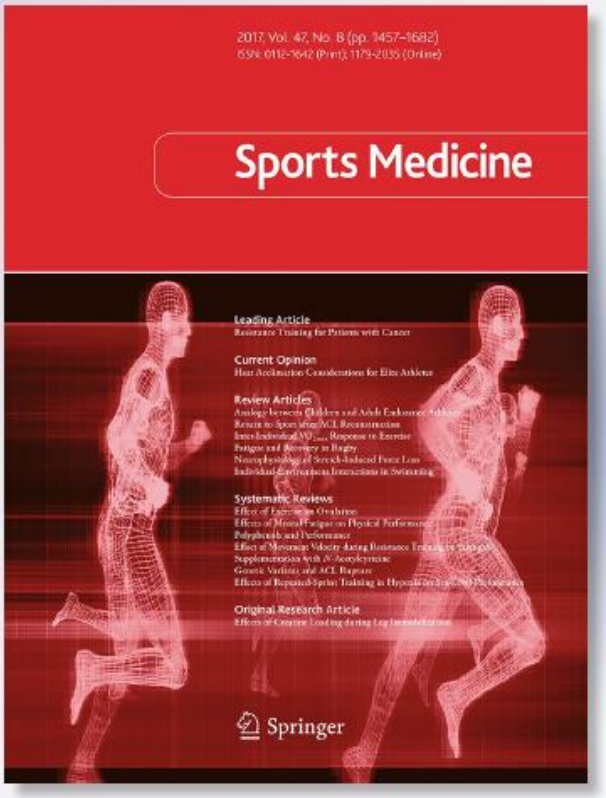

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REVIEW ARTICLE

Inter-Individual Responses of Maximal Oxygen Uptake to Exercise Training: A Critical Review

Philip J. Williamson[1] · Greg Atkinson[1] · Alan M. Batterham[1]

Published online: 17 January 2017

Abstract It has recently been reported how to quantify inter-individual differences in the response to an exercise intervention using the standard deviation of the change scores, as well as how to appraise these differences for clinical relevance. In a parallel-group randomised controlled trial, the key trigger for further investigation into inter-individual responses is when the standard deviation of change in the intervention sample is substantially larger than the same standard deviation derived from a suitable comparator sample. 'True' and clinically relevant inter-individual differences in response can then be plausibly expected, and potential moderators and mediators of the inter-individual differences can be explored. We now aim to critically review the research on the inter-individual differences in response to exercise training, focusing on maximal oxygen uptake (VO_2max). A literature search through the relevant bibliographic databases resulted in the identification of six relevant studies that were published prior to the influential HEalth, RIsk factors, exercise Training And GEnetics (HERITAGE) Family Study. Only one of these studies was found to include a comparator arm. Re-analysis of the data from this study, accounting for random within-subjects variation, revealed an absence of clinically important inter-individual differences in the response of VO_2max to exercise training. The standard deviation of change was, in fact, larger (±5.6 mL/kg/min) for the comparator than the intervention group (±3.7 mL/kg/min). We located over 180 publications that resulted from the HERITAGE Family Study, but we could not find a comparator arm in any of these studies. Some authors did not explain this absence, while others reasoned that only inter-individual differences in exercise response were of interest, thus the intervention sample was investigated solely. We also found this absence of a comparator sample in on-going studies. A perceived high test–retest reliability is offered as a justification for the absence of a comparator arm, but the test–retest reliability analysis for the HERITAGE Family Study was over a much shorter term than the length of the actual training period between baseline and follow-up measurements of VO_2max. We also scrutinised the studies in which twins have been investigated, resulting in concerns about how genetic influences on the magnitude of general within-subjects variability has been partitioned out (again in the absence of a comparator no-training group), as well as with the intra-class correlation coefficient approach to data analysis. Twin pairs were found to be sometimes heterogeneous for the obviously influential factors of sex, age and fitness, thereby inflating an unadjusted coefficient. We conclude that most studies on inter-individual differences in VO_2max response to exercise training have no comparator sample. Therefore, true inter-individual differences in response cannot be quantified, let alone appraised for clinical relevance. For those studies with a comparator sample, we found that the inter-individual differences in training response were not larger than random within-subjects variation in VO_2max over the same time period as the training intervention.

✉ Philip J. Williamson
P.Williamson@tees.ac.uk

[1] Health and Social Care Institute, Teesside University, Middlesbrough TS1 3BX, UK

Key Points

Researchers often focus upon 'main effects' and mean group changes, but these statistics may hide a wide range of responses.

True inter-individual differences in exercise training response can be precisely quantified and appraised for clinical importance only with parallel information from a suitable comparator group or data from a relevant reliability study. Importantly, none of the studies resulting from the HEalth, RIsk factors, exercise Training And GEnetics (HERITAGE) Family Study included a comparator sample.

We provide a 'road map' for the study of inter-individual differences in the responses to exercise training.

1 Introduction

Interest in the concept of individualised responses to an intervention as part of 'personalised medicine' and 'precision care' has been growing over the last 30 years [1–11]. In pharmacogenetics, there has been particular interest in 'tailor-made' drugs and therapies, based on the individual response of a patient and/or certain moderators and mediators of that response [8, 12]. Personalised medicine has also been considered in the context of inter-individual differences in the response of health outcomes to various exercise interventions.

It has been highlighted that the majority of researchers focus upon 'main effects' and mean group changes [13]. These statistics are useful, but do not allow us to distinguish between cases [14], may hide a wide range of responses [15] and have previously been described as misleading [13, 16]. True inter-individual differences in the response to an intervention are less frequently reported, even though it has been proposed that there is large inter-individual variability in response to physical activity interventions [1–6, 13, 17].

Importantly, even in the studies in which inter-individual differences in the response to exercise training are considered, concerns have been levelled at the designs and analysis approaches in these studies [18, 19]. Therefore, it is important at this time for the claims of inter-individual differences in response to an exercise intervention, with a particular focus on maximal oxygen uptake (VO_2max), to be scrutinised in the context of these recent criticisms. Consequently, we have undertaken the present critical review on the HEalth, RIsk factors, exercise Training And GEnetics (HERITAGE) Family Study, as well as the studies that preceded it and the more recently published research. We focus especially on any apparent limitations of previously adopted data analysis approaches, and how researchers have investigated potential moderators and mediators of the inter-individual difference in VO_2max response to an exercise intervention. Finally, we present what we consider to be an appropriate trial design and analysis approach to quantify and make inferences from true inter-individual differences in VO_2max response to exercise interventions. Our focus in this regard is on parallel-group randomised controlled trials (RCTs), as we believe that this design is more widely applicable to research questions addressing chronic adaptations to training. Moreover, published chronic training studies with VO_2max as the outcome are exclusively before-and-after designs, either with or without a control group, with a single intervention period. However, we acknowledge that other designs and statistical approaches have been proposed for quantifying individual differences in response to treatments, primarily the multi-period (replicate) crossover design [20, 21].

2 Maximal Oxygen Uptake and Precision Medicine

Low cardiorespiratory fitness has been established as an independent predictor of all-cause mortality and cardiovascular disease [22, 23]. Many researchers have highlighted the favourable changes in risk factors that occur following a period of exercise training [24–27]. In a large sample of men, a one metabolic equivalent (MET) increase in cardiorespiratory fitness (3.5 ml/kg/min [28]) resulted in a 12% relative risk reduction in all-cause mortality [24].

While a multitude of phenotypes have been investigated, VO_2max response has often been the focus for authors observing the inter-individual variation in response to exercise. Wide inter-individual differences in the trainability of the cardiorespiratory system have been claimed [3, 29, 30], with reports that the improvements in VO_2max range from zero to a 40% increase [29]. Such variation is consistent with the fact that biochemical and physiological functions vary in all humans [31]. Several researchers have also reported that some individuals show little or no improvement in markers such as lipolytic activity, insulin sensitivity, maximal work rate, submaximal exercise heart rate and respiratory exchange rate following an exercise intervention [2–6]. Conversely, it has been proposed that physical activity may increase cardiovascular risk in some individuals, worsening risk factors beyond measurement

error and biological variation [32], although this notion is not consistent with the results of a more recent study [33].

Prescription of exercise is often undertaken with a global approach rather than a personalised one, and as exercise interventions are often used to reduce or prevent age-related reduction in function or lifestyle-related diseases, attention should be paid to the response of each participant within a study [34]. If an individual is likely to respond favourably to a given stimulus, he/she may more likely to engage with that mode of exercise. Consequently, identifying individuals likely to gain greatest benefit would allow practitioners to also focus on alternative exercise, dietary or pharmacological options for those that may be less likely to respond [35, 36].

3 A Critical Review of the Relevant Studies

Via a search of the relevant literature databases, we aimed to locate all the studies in which inter-individual differences in the response of VO_2max to an exercise intervention have been considered. We were particularly interested in ascertaining how many of these studies incorporated a relevant comparator sample into their design. Data from this sample have been deemed to be important for precise quantification and interpretation of inter-individual differences in response [18, 19]. Without these data, measurement error and random or biological variation in the study outcome over time can compromise the quantification of true inter-individual differences in response [33]. Importantly, any physiological outcome can show substantial natural variability over a 4- to 6-month follow-up period in a control sample that does not receive the intervention [33]. This variation will also be present in the intervention group, irrespective of the additional influence of the intervention itself.

3.1 Pre-HERITAGE Studies

The seminal studies on this topic were conducted in the 1980s, with the aim of identifying the inter-individual response to exercise and to clarify the genotype dependency of the modulation of response [1–6] (Table 1). The effects of a 20-week endurance training programme on maximal aerobic power (MAP), ventilatory aerobic threshold and ventilatory anaerobic threshold in ten pairs of monozygotic twins were initially investigated [1]. Unlike in later studies, a comparator (no-exercise training) group was included in this study. From the intra-class correlations (ICCs) reported, the authors described a highly variable response to training and concluded that sensitivity to training is genotype dependent. The authors estimated that 20–25% of training-induced variation in MAP was owing to within-pair differences. Nevertheless, using the approach recently described [19], re-analysis of the data presented in Table 1 of this study revealed no clinically important differences in the standard deviation (SD) of the change scores between the groups (control ± 5.6 mL/kg/min, intervention ± 3.7 mL/kg/min). This observation indicates that there are no substantial inter-individual differences in response to the intervention [19]. In fact, these SDs indicate greater variability in response in the control group vs. the intervention group. We have argued previously that this phenomenon may be due to imprecision in the estimation of inter-individual responses with inadequate sample sizes and/or caused by the intervention having a 'homogenizing' effect on the outcome variable, thus reducing the SD of the changes relative to the control group [19].

Further research was undertaken [2–6, 37], with the study authors claiming there to be large variations in response to exercise for a number of phenotypes, including adipose tissue, fat cell weight, lipolytic activity, glucose conversion into fat cell, triglycerides, skinfolds, percentage body fat, anaerobic, alactic and lactic acid capabilities, fibre type, enzyme activity, sensitivity of muscle characteristics and aerobic endurance performance. Crucially, no comparator group was included in these studies.

A variation in improvement in maximal aerobic performance of between 5 and 88% that was not correlated with a similarly wide range of 16–97% increases in total work output accomplished in a 90-min ergocycle performance test was reported in one study [3]. Inter-individual responses were concluded following the observation of greater between-pair variation than within-pair variation in monozygotic twins, and through sex differences in those studies using mixed-sex cohorts [2]. Genotype-dependent responses for both MAP and endurance performance were observed in conjunction with skeletal muscle enzyme changes following a 15-week training programme [5], while inter-individual differences in anaerobic alactic and lactic acid responses, fibre-type changes and enzyme activity were reported in response to high-intensity intermittent training [6]. Alactic acid and enzyme activity were said to be determined by genotype, although no such relationship was observed for other measured variables. The use of siblings was used to make inferences about the importance of genetic influence in heritability, with *F*-ratios suggesting five to ten times more variance between twin pairs than within pairs. Similarly, genetic determination has been claimed for several different aerobic performance measures from the results of studies in which brothers, monozygotic and dizygotic twins were compared [37]. Changes in aerobic fitness ranging from 0 to 58% were later reported among adults aged 60–71 years, where a trend for older participants improving less than younger subjects was observed [38].

Table 1 Early studies presenting inter-individual responses to exercise interventions

Study, year	Subjects/groups	Exercise training programme			Results	
		Mode	Length (weeks)	Intensity/ frequency/duration/volume	Δ BW/VO_2max/lipids	Other
Prud'Homme et al. [1], (1984)	$n = 48$ [10 pr (6 M, 4 F) MZ twins and 14 (7 M, 7 F) control]	Cycling	20	4–5 days/week; 40–45 min; 60–85% HRR	Variable response, claims that sensitivity to training is genotype dependent	20–25% of training-induced variation in MAP due to within-pair differences
Despres et al. [2], (1984)	$n = 22$ (11 M, 11 F)	Cycling	20	4–5 days/week; 40 min; 80% MHR	No Δ in fat cell number. Δ fat cell weight. Δ lipolysis	Δ lipolysis response greater in male than female individuals. Female individuals had no Δ in fat mass and skinfolds. Increased MAP
Lortie et al. [3], (1984)	$n = 24$ (13 F, 11 M)	Cycling	20	4–5 days/week; 40–45 min; 60–85% HRR	Δ MAP/kg 33%; Δ MAC/kg by 51%; male individuals Δ in MAC/kg 50% more than female individuals	Range of variation: 5–88% Δ MAP/kg and 16–97% Δ MAC/kg
Savard et al. [4], (1985)	$n = 24$ (13 F, 11 M)	Cycling	20	4–5 days/week; 40–45 min; 60–85% HRR	Δ Insulin-stimulated glucose conversion to triglycerides. Δ in male but not female individuals. Similar Δ in MAP	Suggests Δ in modification of fat cell glucose metabolism
Hamel et al. [5], (1986)	$n = 12$ (6 prs MZ twins)	Cycling	15	3–5 days/week; 30–45 min; 60–85% HRR including 1/week HIIT; 3 × 10 min; 80–85% with 5 min recovery	Δ in aerobic enzyme activity in weeks 8–15. 5–11 × more variation between than within pairs	No fibre type Δ
Simoneau et al. [6], (1986)	$n = 28$ [14 pr MZ twins, (7 M pr, 7 F pr)]	Cycling	15	4–5 days/week; HIIT 10 × 15–30 s and 4–5 × 60–90 s; HR recovery to 120–130 b.min efforts	Δ T1 fibres, AAC, ALC, enzyme activity and T2 fibres	Large inter-individual differences, but similar within twins. Genotype suggested as responsible for responsiveness to HIIT on several variables. 65% of ALC associated with genotype Δ oxidation following HIIT. Fibre-type changes independent of genotype

AAC anaerobic alactic acid, *ALC* anaerobic lactic acid, *b.min* beats per minute, *BW* body weight, *F* female, *HIIT* high-intensity interval training, *HR* heart rate, *HRR* heart rate reserve, *M* male, *MAP* maximal aerobic power, *MHR* maximal heart rate, *MZ* monozygotic, *Pr* pair, *SD* standard deviation, *VO_2max* maximal oxygen uptake

The justification for the lack of a non-exercising control in the subsequent HERITAGE Family Study, which appears to have been continued through subsequent investigations, was based on an observation of mean values from previously studied control groups remaining unchanged [39]. However, a finding of no substantial change in the mean for the control group can occur in the face of substantial random within-subject variability in the changes in VO_2max over the duration of the study. The variability in the changes in the intervention group must be assessed against the backdrop of this natural variability. In a RCT, the mean effect of the intervention is given by the mean change in the intervention minus the mean change in the control. This logic should be extended to the assessment of inter-individual responses to an exercise intervention. In a parallel-group RCT, one cannot say with 100% certainty whether any specific individual in the intervention group is a positive responder, as what would have happened to that person if, contrary to the fact, they had been in the control group, is unknown. This is the fundamental counterfactual basis of the RCT.

However, if the variance in the response in the intervention group is substantially greater than that in the control arm, then true individual responses may be inferred. The control group variability over the same time period as the intervention effectively provides our best guess of the counterfactual—what would have happened to individuals in the intervention group if they had been in the control arm. In parallel-group RCTs, substantially greater response variance in the intervention group vs. the control is both necessary and sufficient for inferring true inter-individual differences in response to the intervention. Assuming that sample estimates are accurate estimates of the population values, it is incontrovertible that there must be a larger variance in response in the intervention vs. the control if true individual differences exist in response to treatment. Furthermore, although a parallel-group RCT cannot isolate variance owing to subject-by-treatment interaction [21], in this design, a greater response variance in the intervention vs. the control is sufficient to infer inter-individual responses. As described in Sect. 4, for any individual in the intervention arm we can then derive the probability of being a positive responder/trivial responder/or negative responder.

3.2 Recent Studies

Six to nine times more variance in VO_2max response between monozygotic twin pairs than within pairs has been reported [40]. This and other studies were described as "standardized and carefully monitored" [9], with a "careful and constant program of quality control and assurance" [41]; yet they still lack a suitable comparator sample. Nevertheless, RCTs are not only relevant to the investigation of main effects [20]. Use of the intervention-only arm as a basis for analysis is problematic, as similar or even greater variability of changes may also be observed in a control group, as was the case when a previous study was re-examined [1]. We fear that too much emphasis has been placed on gene relationship statistics without answering the initial and crucial question of whether clinically relevant inter-individual differences in responses exist. This question is answered by calculating the difference in baseline to follow-up variability between intervention and comparator groups, and comparing this difference to a rationalised minimum clinically important difference (MCID) [19].

More recently, large variations in VO_2max response to exercise were reported in the large scale Dose–Response to Exercise in Women (DREW) Study [42]. A decrease in the prevalence of non-response with increased training volume was also observed. The authors reported a large amount of inter-individual variability (−33.2 to 76.0% change), citing baseline VO_2max, age and training volume as predictors of non-response. The study comprised three intervention groups (4, 8 and 12 kcal/kg per week of exercise) alongside a control group, with a stated purpose of the analysis to examine the determinants of change in VO_2max in response to exercise training. However, the decision to exclude the control group from the analysis compromised the correct quantification of the true inter-individual response and missed potentially vital information. Further work from the DREW study reported that 30% of participants experienced no improvement in maximal aerobic performance [43]. However, once again, no control group data were studied.

Recent studies have been undertaken to further identify possible genotype or phenotype interactions responsible for moderating the magnitude of inter-individual response [15, 17, 44]. Large variation in training response to an 8-week aerobic endurance training intervention was reported [17]. Interestingly, whilst a control group was used, the baseline to follow-up changes in this group was not used for comparison at all. As we have stated, disregarding the control group in this manner, on the basis that there will be no mean change and/or the short-term test–retest reliability is high, is a flawed approach. Differences in response were observed by dividing the intervention group responses by quartile, rather than retaining a continuous variable; this approach discards information and has previously been reported to be an inadequate analysis method in epidemiology [45]. Upon closer inspection, in contrast to the authors' assertion of the differential effects of the training protocol on the sympathetic nervous system, it appears that there may be little true difference in the variation (standard deviation of change) between each of the 'response' groups.

3.3 Concurrent Training

Investigations into the inter-individual responses to combined endurance and strength training in young [46] and older adults [15] have also been undertaken. The findings of these studies are in general agreement with much of the previously published literature, in that a range of training responses were observed. Nevertheless, as in an earlier study [1], a control group was included in one study [15] but no specific comparison was made. It is also apparent from the responses reported in Fig. 1 of this investigation [15] that similar variation in response exists in the control group as in the experimental groups, reinforcing the view that there is similar variability of baseline to follow-up changes across all groups. The participants in another study acted as their own control in a crossover trial [46]; however, the residual training effect of the intervention period on the response following the washout period is unknown.

3.4 Biological Variability

Not all inter-individual responses may be due to the factors postulated in the studies reviewed within this article. Neither does variation in responses confirm that this assumption of inter-individual difference in response is true for any particular study [19]. Small day-to-day changes cannot be classified as a worthwhile change, and the response must be clinically relevant and more than the natural biological variation between baseline and follow-up measurements [47]. Of course, patients differ not only by genetics, but also by their personal history and environmental circumstances [48], and this can lead to a multitude of effects on inter-individual response. There appears to be little doubt that the response to exercise training is influenced by multiple factors.

A new focus on the quantification of true inter-individual differences and the moderators and mediators responsible may, therefore, have substantial clinical relevance, with any correctly quantified heterogeneity affording the opportunity to identify possible molecular determinants [49]. Indeed, RNA profiling may be a potential methodology for capturing information critical to informing the integrated physiological response and molecular determinants [36], once the presence of inter-individual variation in response has been confirmed.

3.5 Identifying 'Responders' and 'Non-Responders'

A further limitation of much of the previous research is the classification of individuals as 'non-responders' [49, 50] without first defining the term, although this has been partially addressed more recently when defined as those improving by "less than the natural biological variability of the selected variable" [47]. Strictly, a positive response should be defined as an increase that is greater than the MCID. For VO_2max, for example, the MCID could be defined as 1 MET, anchored to a clinically relevant relative risk reduction for all-cause mortality of around 12% for this value [24]. For a given individual, the observed change in VO_2max after the intervention can be combined with knowledge of the natural random variation of VO_2max over the same time period (from a control group or similar reliability study) to derive the probability that this individual's true response is greater than the MCID [18]. We can then more properly describe each individual in the intervention as, for example, 'likely to be a responder', 'very unlikely to be a responder' or 'possibly a negative responder'.

Similarly to previous reports [42], further argument for the dose response to exercise is observed when greater exercise volume [43] or intensity [44] was associated with reduced chances of being classified as a non-responder. While direct comparison between studies is not straightforward, these and similar findings suggest that some people may be more sensitive to dose prescription of exercise, as opposed to being non-responsive. If this is the case, effective identification of dose requirement or requirement for multimodal approaches such as concurrent training may provide a capability for enhancing the efficacy of an intervention [51]. However, as is covered in this review, we argue that an individual cannot be categorically defined as a 'responder' or other such descriptor; merely a probability (percentage chance) that they are such can be applied to each individual [18]. Even with this information, in a single-period, before-and-after study design, this process can only occur in the presence of an appropriate comparator group assessed over the same or very similar time period as the exercise intervention.

3.6 The HERITAGE Family Study

The large-scale, longitudinal, multicentre HERITAGE Family Study was initiated to investigate and identify the role of the genotype in cardiovascular, metabolic and hormonal responses to a 20-week aerobic exercise training programme [52]. The contribution of regular exercise to changes in cardiovascular disease and diabetes mellitus risk factors was also investigated [41, 52]. To date, 186 separate publications have resulted from the study, with some of these involving the comparison of various familial relationships to determine the relative importance of genetics [53–55]. The bulk of the research undertaken during the HERITAGE Family Study asserts that there are no genotype-specific covariate effects on VO_2max response, such as age, sex or weight [13, 30, 50]. Familial aggregation was reported in response to maximal

[3, 49, 56] and submaximal [54, 57] aerobic training, with two and a half times more variance reported between than within families for the VO_2max response.

A reported genetic contribution of approximately 47% [49, 55] of the variance observed in the VO_2max training response from the HERITAGE studies was similar to that previously reported [3, 58]. These data were characterised by a strong maternal aggregation [49, 54, 56], with shared environmental factors also contributing to the observed heritabilities. The mechanisms underpinning this variance are unclear, but suggestions of genetic contribution from mitochondrial DNA [49] or the expression of genes inherited from the mother have been presented [54]. Correlations between spouses have led to familial environmental factors also being postulated as responsible for some of the variance observed in response to exercise [54, 56, 58, 59]; however, the correlations presented are small ($r = 0.14$–0.26); therefore, posing, rather than answering, further questions on this issue. The crucial question that is, again, unanswered in the absence of a comparator group is whether there are genetic influences on the individual magnitude of random within-subjects variability. If this is known, then these genetic influences could be quantified.

In the HERITAGE studies, it is claimed that there is considerable variation in response. Nevertheless, it remains unclear as to whether it was the same individuals that showed no response for all measures, or if each individual showed differing response characteristics across the spectrum of physiological markers investigated. Recent research has attempted to elucidate this issue, observing improvements in at least one measured variable in every individual [47], though again, this study is limited by the lack of a control group with which to compare the inter-individual response. Interestingly, despite methodological concerns, individuals with the highest response to endurance training have also shown a high response to resistance training, but the reverse was not true [46]. This area opens up future avenues in which to investigate the magnitude of response, in the presence of proper initial quantification through comparison with a suitable comparator sample.

3.7 Twin Studies

Previously noted criticisms of twin studies point to the fact that they may not necessarily separate genetic from environmental pathways [60]. Presentation of evidence of genetic variance of numerous phenotypes through greater between-twin pair variance than within-pair variance is often reported through the use of ICCs [1, 5, 36, 61–66] (Table 2). These observations are highly sample specific, and a comparison of the ICCs between studies is not without difficulty, owing to the heterogeneity of samples. The potential for ICCs in twin studies to overestimate heritability has also been highlighted in that genetic and environmental factors have not been adequately separated [63].

It is as yet unknown as to whether any relationship between genes and phenotype is even linear [60] and while genetic variation is not denied in this review, it is not clear that all observed variance is genetic [48]. We believe that when analysing such a design, it would be more appropriate to use data from a relevant control (no-exercise) sample and a linear mixed model to correctly quantify the influence of genetics on magnitude of response. Associations could then be presented as a regression coefficient in the units of measurement, rather than a comparison of correlation values. In this way, the clinical importance of any association can be inferred.

Common underlying environmental effects have also been proposed as being underestimated because of the study design or low statistical power [67]. Adoption studies combined with twin studies to compare identical and fraternal twins and twins reared apart [63] and repeated assessments [20] may be required to quantify some of these issues.

3.8 Baseline Correlation of Changes

Several authors of the HERITAGE studies correlated each individual's baseline score with the follow-up change to attempt to determine the contribution of baseline status to the inter-individual response to exercise training. From such analyses, it has also been reported that age, sex, fat mass, fat-free mass, weight and race have little or no impact upon the inter-individual response to training or covariate effect [13, 30], and that the initial level of the phenotype was a major determinant of the magnitude of response in some cases [13]. Nevertheless, this correlation approach has been questioned, owing to regression to the mean and mathematical coupling influences [68]. Linear mixed-effects modelling and other methods such as that previously reported [69] have been purported to be superior to this simple correlation approach [68].

3.9 Testing Quality Control

The HERITAGE intervention was described as having a careful and constant programme of quality control and quality assurance [41]. Nevertheless, this claim was based on the test–retest mean differences being small, although the selection of either an average of two VO_2max test scores (where the coefficient of variation was less than 5% between the two) or the higher score (if the coefficient of variation was greater than 5% between the two) at both

Table 2 Twin studies presenting intra-class correlations in analysis of inter-individual responses to exercise interventions

Study, year	Number of twin pairs	Mean (SD) age (years)	Outcome measures	ICC	Age/sex adjustment
Prud'homme et al. [1], (1984)	10 MZ (6 F, 4 M)	20 (2.9)	MAP, VAT, VANT	0.24 to 0.74	Not reported
Hamel et al. [5], (1986)	6 MZ (3 M, 3 F)	21 (4)	VO_2max	0.69	Not reported
Bouchard et al. [36], (1986)	53 MZ (mixed sex)	16–34 (range)	VO_2max	0.85	Yes
	33 DZ (mixed sex)			0.74	
	27 male siblings			0.55	
Poehlman et al. [61], (1986)	6 MZ male individuals	19.2 (2.3)	Body composition, fat morphology, fat mass, skinfolds	0.46 to 0.90	Not reported
Bouchard et al. [62], (1990)	12 MZ male individuals	21 (2)	Body composition and fat topography	0.4 to 0.55	Not reported
Heller et al. [63], (1993)	46 MZA	52–86 (range)	Lipids	0.22 to 0.79	Dichotomous age categories
	7 MZT			0.33 to 0.83	
	100 DZA			−0.06 to 0.47	
	89 DZT			−0.13 to 0.49	
Bouchard et al. [64], (1994)	7 MZ male individuals	21 (0.8)	Body weight, FFM, topography, VO_2max	0.25 to 0.87	No mention: single sex, low SD of age
Hong et al. [65], (1997)	289 pr; 45 MZA		Insulin, glucose, lipids, BP	0.28 to 0.64	Yes
	64 MZT			0.56 to 0.6	
	95 DZA			0.17 to 0.39	
	85 DZT			0.15 to 0.26	
Tremblay et al. [66], (1997)	11pr MZ male individuals	21 (0.8)	RMR, fat loss, weight loss, FFM loss	0.32–0.69	Single sex, low SD of age

BP blood pressure, *DZ* dizygotic, *DZA* dizygotic twins reared apart, *DZT* dizygotic twins reared together, *F* female, *FFM* fat-free mass, *ICC* intra-class correlation, *M* male, *MAP* maximal aerobic power, *MZ* monozygotic, *MZA* monozygotic twins reared apart, *MZT* monozygotic twins reared together, *pr* pair, *RMR* resting metabolic rate, *SD* standard deviation, *VANT* ventilatory anaerobic threshold, *VAT* ventilatory aerobic threshold, VO_2max maximal oxygen uptake

baseline and follow-up [70] could have led to inconsistent data. To accurately analyse the data, identical methodology should ideally be used for all participants. Test–retest reliability was reported to be 4.1–5.0% and ICCs of 0.96–0.97 were reported over a period of 2 days [70] and 2 weeks [71], implying adequate short-term reproducibility. It is our belief that reproducibility needs to be assessed over a longer period, preferably matching the length of the intervention, to estimate the true extent of longer-term, within-subject variation.

A better alternative is to use an RCT design, wherein the control group in effect acts as the perfect contemporaneous reliability study. Each of the investigations discussed has contained a single application of an intervention (single-period, before-and-after study). We reiterate that the primary limitation of the parallel-group RCT design in permitting the quantification of inter-individual variation in treatment response is that it does not allow the isolation of the variance because of true subject-by-treatment interaction [21]. In this design, the SD for inter-individual responses, although free from random error, includes the subject-by-treatment interaction plus any within-subject variability in treatment response introduced by the intervention [20]. Indeed, the multi-period (replicate) crossover study, in which participants are randomised to sequences in which they receive both the intervention and comparator treatments in at least two periods each, is the only design that can identify variance between treatments, between subjects and in the subject-by-treatment interaction [20]. However, the primary limitation of the replicate crossover, in the context of chronic training studies, is the long and uncertain washout periods required and hence potentially substantial carryover effects [18].

The authors of a recent investigation into the cardiac determinants of individual response in change in aerobic fitness after a moderate-intensity exercise intervention [43] stated that they incorporated "well-controlled exercise trials" in keeping with the HERITAGE Family Study.

Nevertheless, 'well-controlled' appears to refer to relatively short-term repeatability of measurements (over a few days) rather than the within-subjects variability in measurements over the duration of the intervention (a few months). Just because a measurement method has good short-term repeatability does not rectify the problem of a lack of a control group, which must be employed to make a formal comparison of the variability of the change scores in intervention vs. control groups.

Consequently, the inclusion of data from studies such as these is potentially misleading, and as such, participants from these studies that have been termed 'responders' and 'non-responders' may have been selected for further investigation as to the potential moderators and mediators of the inter-individual response, when it may be nothing other than their natural biological variation that has been measured.

3.10 *N*-of-1 Trials

In pharmacogenetics, *n*-of-1 trials have been proposed [72, 73], but these single-subject trial studies have previously been linked to controversial issues in clinical investigation, such as carryover effects and the presupposition of patient-by-treatment interaction and behavioural change [74], which may confound the effectiveness of interventions. Of course, if a number of *n*-of-1 trials are carried out, then the combined data effectively equate to the repeated period crossover design proposed by Hecksteden et al. [20]. It has also been proposed that *n*-of-1 data with a limited observation count per participant may not be compatible with statistical models that aim to identify the inter-individual response and may be preferential for estimating the population effect [75].

4 A Road Map for Future Study Designs and Analyses

Recently, for both parallel-group and replicate crossover designs, more appropriate and robust statistical approaches have been forwarded for the quantification of a true inter-individual response to a treatment. Relevant sources of variability must first be quantified [20] before any exploration is undertaken of the true inter-individual variation in treatment response. Additionally, without knowledge of the smallest worthwhile change or the MCID, no substantial inter-individual differences in VO_2max response to an exercise intervention can be claimed. When analysing the collected data from a parallel-group RCT, it has been proposed that comparing the SD of the intervention arm of the study against the SD of the comparator arm, using $SD_R = \sqrt{SD_I^2 - SD_C^2}$, where R is the inter-individual responses, I is the intervention sample SD and C is the comparator sample SD [18, 19], provides a more accurate statistical analysis of the presence of inter-individual differences in response. If appropriate clinical inferences are to be made about the magnitude of change and any inter-individual response to the intervention, SDs, confidence intervals, effect sizes and magnitude-based inferences should also be interpreted [18, 76]. Using a custom spreadsheet [77], and with knowledge of the typical error over the same timeframe as the intervention and the smallest worthwhile change, the probability (percentage chance) of each individual being a responder can be calculated and the individual classified as 'very likely', 'likely', 'possibly', 'possibly not', 'unlikely' and 'very unlikely' to be a responder. This is a more robust approach, as the standard parallel-arm study design renders the definitive identification of specific individuals as non-responders impossible [33]. For instance, individuals could be termed likely 'positive' responders if the individual probabilities were above 0.75 (75% chance, or odds of 3:1 in favour) and the converse for 'negative' responders. A finding of substantial clinically relevant inter-individual differences in response to the intervention would justify further investigation of potential moderators and mediators, using more advanced statistical modelling.

If we consider the original pre-HERITAGE study [1], the mean VO_2max improvement in the exercise intervention group was 5.5 (±3.7) mL/kg/min and the change in the control group was −0.6 (± 5.6) mL/kg/min. The pooled between-subjects SD for VO_2max at baseline was 5.9 mL/kg/min. If we define a 'responder' by an improvement of 1 MET, an individual would be required to improve by 7.4 mL/kg/min (i.e. approximately 1.25 SDs) for the probability of being a true responder to be 0.75. To increase confidence, using a probability of 0.95 (i.e. 'very likely' to be a responder), the individual would be required to improve by 13.5 mL/kg/min, or more than 2 SDs. Therefore, an individual who showed an improvement of, for example, 5 mL/kg/min (a figure above the clinically relevant threshold for a responder of 1 MET) would have a probability of 0.60 of being a true responder. Obviously, in this case, this is little better than chance. These figures demonstrate that an individual would be required to improve their VO_2max substantially more than the MCID (i.e. 1 MET) to be deemed likely or very likely to be a responder. This is in stark contrast to the practice of classification of any individual showing improvement of 3.5 mL/kg/min (1 MET) or more as a definite responder. Assuming normal distribution of the changes in the control group and a MCID of 1 MET, the mean and SD reveal that 23% of the control group would be expected to 'improve' by more than 1 MET, and would be labelled conventionally as 'positive responders'. These apparent positive responses

in the control are due to the random variation in VO_2max over a 20-week period. As highlighted, the SD of the change scores in each group reveal that there are no substantial inter-individual responses in the intervention group (vs. control), and any further investigation of the mechanisms underpinning inter-individual responses is therefore unwarranted.

In contrast to our proposed approach, it has been argued that a large-scale, multi-period, crossover training study approach is a more robust method of predicting training response [20]. This approach, however, presents a number of challenges. Given the difficulties of recruiting the sample size required for a large-scale training study, this type of study is likely to be statistically underpowered, while the time required to run a training intervention study, complete with washout periods, is highly restrictive. The crossover trial methodology might also have less relevance in training studies than in pharmacological research, as the effectiveness of any washout period is unknown, and may diminish training-related effects. This approach has been previously used through the use of a 2-month washout period subsequent to a 2-week intervention [46], but the effects of the previous training intervention cannot be controlled for, and therefore each participant is potentially beginning from a different baseline. Unlike in pharmacological studies, where the washout period for a specific drugs is defined as some multiple of the drug's half-life, it cannot be stated with any certainty that a previous period of training or an exercise intervention has not changed the individual at the cellular or neuromuscular level. This

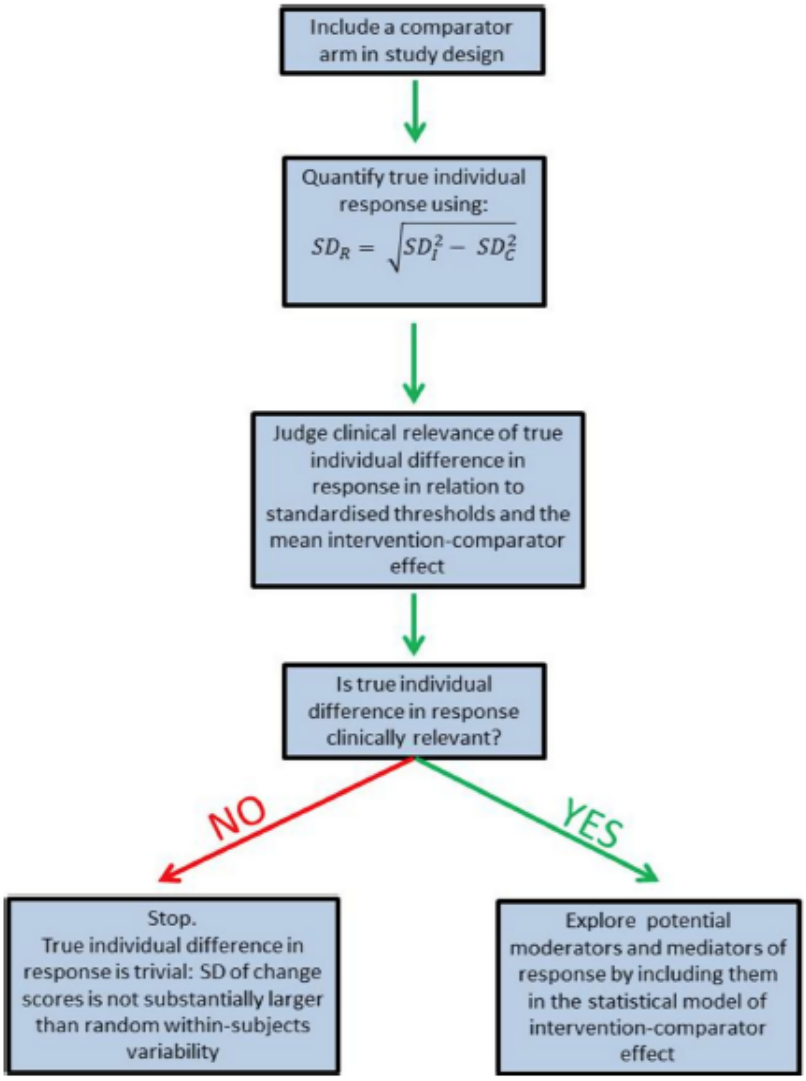

Fig. 1 Conceptual framework for the quantification of true inter-individual differences in response to an exercise intervention [19]. *SD* standard deviation, SD_C standard deviation of the pre-to-post change score of the comparator arm, SD_I standard deviation of the pre-to-post change score of the intervention arm, SD_R standard deviation of the true inter-individual response of the intervention

problem leads to a sample that is not acting as its own control, and therefore presents potential differences at baseline for each intervention period. The multi-period crossover design might be more applicable to the investigation of acute effects of short-term interventions [15]. There are also a multitude of sources of variability that create challenges in identifying true inter-individual differences in response, such as maturation, diet modulation, disease, lifestyle and environment to be accounted for, further confounding the issue [51].

5 Conclusions

To date, the investigation of inter-individual differences in VO_2max response to exercise training has been conducted almost exclusively without a control group or comparator arm. While we do not deny that the identification of any inter-individual response to an exercise intervention is important, we maintain that the variation must be appropriately quantified prior to deeper investigation, and we recognise that a number of challenges exist in realising this goal. Primary among these is the proper quantification and determination of a threshold for meaningful magnitude of change, to establish the presence of clinically important differences in response [51]. To quantify the inter-individual response to an exercise intervention, studies should contain the presence of a comparator arm, preferably as an RCT design. A number of variables and health outcomes should also be collected, as some participants may improve across some but not all physiological measures. Furthermore, the correct statistical analysis and modelling must be used to identify the presence of a true, clinically relevant individual response, as unless a true inter-individual response exists, it is futile looking for treatment interactions [14].

Future work on any primary outcome in exercise intervention trials should focus upon a thorough systematic review of the available literature, to determine the robustness of the published data addressing inter-individual differences in response to exercise training. Secondary analysis of the data presented by fellow researchers should also be undertaken, to quantify inter-individual responses in previous trials. Only when these effects have been properly quantified, using the SD of the change score after adjusting for random within-subjects variability using the following equation: $SD_R = \sqrt{SD_T^2 - SD_C^2}$ [18, 19], can the design of experiments to further elucidate the mechanisms responsible for the individual response be confirmed. Supplementary investigations and robust data analysis must then be carried out, using a logical framework (Fig. 1) such as that previously proposed [19] to properly identify whether specific moderators and mediators exist that control the likelihood of an individual responding to an exercise intervention, rather than looking to unravel complex gene responses. At this point, when included as covariates, these moderators and mediators may account for the inter-individual response, to the extent that they reduce the magnitude of the SD for inter-individual responses [15].

In summary, against the backdrop of suggestions of precision interventions, individuals may respond to treatment in a variety of ways; the intervention might be beneficial, ineffective or harmful for different people. The issue of inter-individual differences in the response of VO_2max following an exercise intervention is very important, and identifying the personal characteristics that account for these variations in response may ultimately allow more effective direction of interventions. Common themes in previous trial design and data analysis are evident, such as a lack of comparator arm or disregarding data from the control, and the use of ICCs to quantify genotype dependency of inter-individual differences in the variability of VO_2max response. While the subject is an important one, it is crucial that the correct quantification methodology is employed, together with an understanding of the clinical importance of any inter-individual response, before suggestions can be made in regard to potential moderators and mediators responsible for the observed inter-individual variance of VO_2max in response to exercise training.

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References

1. Prud'Homme D, Bouchard C, LeBlanc C, et al. Sensitivity of maximal aerobic power to training is genotype-dependent. Med Sci Sports Exerc. 1984;16:89–93.
2. Despres JP, Bouchard C, Savard R, et al. The effect of a 20-week endurance training program on adipose-tissue morphology and lipolysis in men and women. Metabolism. 1984;33:235–9.
3. Lortie G, Simoneau JA, Hamel P, et al. Responses of maximal aerobic power and capacity to aerobic training. Int J Sports Med. 1984;5:232–6.
4. Savard R, Despres JP, Marcotte M, et al. Endurance training and glucose conversion into triglycerides in human fat cells. J Appl Physiol. 1985;1985(58):230–5.
5. Hamel P, Simoneau J, Lortie G, et al. Heredity and muscle adaptation to endurance training. Med Sci Sports Exerc. 1986;18:690–6.
6. Simoneau JA, Lortie G, Boulay MR, et al. Inheritance of human skeletal muscle and anaerobic capacity adaptation to high-intensity intermittent training. Int J Sports Med. 1986;7:167–71.

7. Rose EA, Partfitt G. A quantitative and qualitative explanation of the individual differences in affective responses to prescribed and self-selected exercise intensities. J Sport Exerc Psychol. 2007;29:281–309.
8. Senn S, Rolfe K, Julious SA. Investigating variability in patient response to treatment: a case study from a replicate cross-over study. Stat Methods Med Res. 2011;20:657–66.
9. Bouchard C. Genomic predictors of trainability. Exp Physiol. 2012;97:347–52.
10. Bouchard C, Antunbes-Correa LM, Ashley EA, et al. Personalised preventive medicine: genetics and the response to regular exercise in preventive interventions. Prog Cardiovasc Dis. 2015;57:337–46.
11. Mann TN, Lamberts RP, Lambert MI. High responders and low responders: factors associated with individual variation in response to standardized training. Sports Med. 2014;44:1113–24.
12. Spear BB, Heath-Chiozzi M, Huff J. Clinical applications of pharmacogenetics. Trends Mol Med. 2001;7:201–4.
13. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. Med Sci Sports Exerc. 2001;33(S6):S452–3.
14. Senn S. Individual response to treatment: is it a valid assumption? BMJ. 2004;329:966–8.
15. Karavirta L, Hakkinen K, Kauhanen A, et al. Individual responses to combined endurance and strength training in older adults. Med Sci Sports Exerc. 2011;43:484–90.
16. Bouchard C. Human adaptability may have a genetic basis. In: Landry F, editor. Health and risk estimation, risk reduction and health promotion. Proceedings of the 18th Annual Meeting of the Society of Prospective Medicine. Ottawa: Canadian Public Health Association; 1983. p. 463–76.
17. Hautala AJ, Makikallio TH, Kiviniemi A, et al. Cardiovascular autonomic function correlates with the response to aerobic training in healthy subjects. Am J Physiol Heart Circ Physiol. 2003;285:1747–52.
18. Hopkins W. Individual responses made easy. J Appl Physiol. 1985;2015(118):1444–6.
19. Atkinson G, Batterham A. True and false interindividual differences in the physiological response to an intervention. Exp Physiol. 2015;100:577–88.
20. Hecksteden A, Krauscher J, Scharhag-Rosenberger F, et al. Individual response to exercise training: a statistical perspective. J Appl Physiol. 1985;2015(118):1450–9.
21. Senn S. Mastering variation: variance components and personalised medicine. Stat Med. 2016;35:966–77.
22. Laukkanen JA, Kurl S, Salonen R, et al. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective, population based cohort study. Eur Heart J. 2004;25:1428–37.
23. Sui X, LaMonte MJ, Blair SN. Cardiorespiratory fitness as a quantitative predictor of non-fatal cardiovascular events in asymptomatic men and women. Am J Epidemiol. 2007;165:413–23.
24. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346:793–801.
25. Church TS, Earnest CP, Skinner JS, et al. Effects of different doses of activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized control trial. JAMA. 2007;297:2081–91.
26. Kelley GA, Kelley KS. Efficacy of aerobic exercise on coronary heart disease risk factors. Prev Cardiol. 2008;11:71–5.
27. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized control trial. JAMA. 2010;304:2253–62.
28. Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990;13:555–65.
29. Bouchard C. Individual differences in the response to regular exercise. Int J Obes Relat Metab Disord. 1995;19(Suppl. 4):S5–8.
30. Feitosa MF, Gaskill SE, Rice T, et al. Major gene effects on exercise ventilatory threshold: the HERITAGE Family Study. J Appl Physiol. 1985;2002(93):1000–6.
31. Vollaard NBJ, Constantin-Teodosiu D, Fredriksson K, et al. Systematic analysis of adaptations in aerobic capacity and submaximal energy metabolism provides a unique insight into determinants of human aerobic performance. J Appl Physiol. 1985;2009(106):1479–86.
32. Bouchard C, Blair CN, Church TS, et al. Adverse metabolic response to regular exercise: is it a rare or common occurrence? PLoS One. 2012;7(5):e37887.
33. Leifer ES, Mikus CR, Karavirta L, et al. Adverse cardiovascular response to aerobic exercise training: is this a concern? Med Sci Sports Exerc. 2015;48:20–5.
34. Kainulainen H. Run more, perform better: old truth revisited. J Appl Physiol. 1985;2009(106):1477–8.
35. Rankinen T, Argyropoulos G, Rice T, et al. CREB1 is a strong genetic predictor of the variation in exercise heart rate response to regular exercise: the HERITAGE Family Study. Circ Cardiovasc Genet. 2010;3:294–9.
36. Timmons JA, Knudsen S, Rankinen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. J Appl Physiol. 1985;2010(108):1487–96.
37. Bouchard C, Lesange R, Lortie G, et al. Aerobic performance in brothers, dizygotic and monozygotic twins. Med Sci Sports Exerc. 1986;18:639–45.
38. Kohrt WM, Malley MT, Coggan AR, et al. Effects of gender, age, and fitness level on response of VO_2max to training in 60–71 year-olds. J Appl Physiol. 1985;1991(71):2004–11.
39. Wilmore JH, Stanforth PR, Gagnon J, et al. Heart rate and blood pressure changes with endurance training: the HERITAGE Family Study. Med Sci Sports Exerc. 2000;33:107–16.
40. Bouchard C, Wolfarth B, Rivera MA, et al. Genetic determinants of endurance performance. In: Shephard RJ, Astrand PO, editors. Endurance in sport: encyclopaedia of sports medicine. Oxford: Blackwell Scientific; 2000. p. 223–42.
41. Gagnon J, Province MA, Bouchard C, et al. The HERITAGE Family Study: quality assurance and quality control. Ann Epidemiol. 1996;6:520–9.
42. Sisson SB, Katzmaryk PT, Earnest CP, et al. Volume of exercise and fitness non-response in sedentary post-menopausal women. Med Sci Sports Exerc. 2009;41:539–45.
43. Pandey A, Ayers C, Blair SN, et al. Cardiac determinants of heterogeneity in fitness change in response to moderate intensity aerobic exercise training. J Am Coll Cardiol. 2015;65:1057–8.
44. Ross R, de Lannoy L, Stotz PJ. Separate effects of intensity and amount of exercise on interindividual cardiorespiratory fitness response. Mayo Clin Proc. 2015;90:1506–14.
45. Bennette C, Vickers A. Against quartiles: catergorization of continuous variables in epidemiologic research, and its discounts. BMC. 2012;12:1. doi:10.1186/1471-2288-12-21.
46. Hautala AJ, Kiviniemi AM, Makikallio TH, et al. Individual differences in the responses to endurance and resistance training. Eur J Appl Physiol. 2006;96:535–42.
47. Scharhag-Rosenberger F, Walitzek S, Kindermann W, et al. Differences in adaptations to 1 year of aerobic endurance training: individual patterns of nonresponse. Scand Med Sci Sports. 2012;22:113–8.
48. Senn S. Individual therapy: new dawn or false dawn? Drug Info J. 2001;35:1479–94.

49. Bouchard C, An P, Rice T, et al. Familial aggregation of VO_2max response to exercise training: results from the HERITAGE study. J Appl Physiol. 1985;1999(87):1003–8.
50. Skinner JS, Jaskolski A, Jaskolska A, et al. Age, sex, race, initial fitness and response to training: the HERITAGE Family Study. J Appl Physiol. 1985;2001(90):1770–6.
51. Buford TW, Roberts MD, Church TS. Toward exercise as personalised medicine. Sports Med. 2013;43:157–65.
52. Bouchard C, Leon AS, Rao DC, et al. The HERITAGE Family Study: aims, design and measurement protocol. Med Sci Sports Exerc. 1995;27:721–9.
53. Bouchard C, Rankinen T, Chagnon YC, et al. Genomic scan for maximal oxygen uptake and its response to training in the HERITAGE Family Study. J Appl Physiol. 1985;2000(88):551–9.
54. Perusse L, Gagnon J, Province MA, et al. Familial aggregation of submaximal aerobic performance in the HERITAGE Family Study. Med Sci Sports Exerc. 2001;33:597–604.
55. Bouchard C, Sarzynski MA, Rice TK, et al. Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. J Appl Physiol. 2011;110:1160–70.
56. Bouchard C, Daw E, Warwick E, et al. Familial resemblance for VO_2max in the sedentary state: the HERITAGE Family Study. Med Sci Sports Exerc. 1998;30:252–8.
57. Gaskill SE, Rice T, Bouchard C, et al. Familial resemblance in ventilatory threshold: the HERITAGE Family Study. Med Sci Sports Exerc. 2001;233:1832–40.
58. Montoye HJ, Gayle R. Familial relationships in maximal oxygen uptake. Hum Biol. 1978;50:241–9.
59. Lesage RJA, Simoneau J, Jobin J, et al. Familial resemblance in maximal heart rate, blood lactate and aerobic power. Hum Hered. 1985;35:182–9.
60. Maes HHM, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet. 1997;27:325–51.
61. Poehlman ET, Tremblay A, Despres JP, et al. Genotype-controlled changes in body composition and fat morphology following overfeeding in twins. Am J Clin Nutr. 1986;43:723–31.
62. Bouchard C, Tremblay A, Despres JP, et al. The response to long-term overfeeding in identical twins. N Engl J Med. 1990;322:1477–82.
63. Heller DA, De Faire U, Pederson NL, et al. Genetic and environmental influences on serum lipid levels in twins. N Engl J Med. 1993;328:1150–6.
64. Bouchard C, Tremblay A, Despres JP, et al. The response to exercise with constant energy intake in identical twins. Obes Res. 1994;2:400–10.
65. Hong Y, Pederson NL, Brismar K, et al. Genetic and environmental architecture of the features of the insulin-resistance syndrome. Am J Hum Genet. 1997;60:143–52.
66. Tremblay A, Poehlman ET, Despres JP, et al. Endurance training with constant energy intake in identical twins: changes over time in energy expenditure and related hormones. Metabolism. 1997;46:499–503.
67. Segal NL, Allison DB. Twins and virtual twins: bases of relative body weight revisited. Int J Obes Metab Disord. 2002;26:437–41.
68. Chiolero A, Paradis G, Rich B, et al. Assessing the relationship between the baseline value of a continuous variable and subsequent change over time. Front Public Health. 2013;1:1–8.
69. Blomqvist N, Svardsudd K. A new method for investigating the relation between change and initial value in longitudinal blood pressure data. II. Comparison with other methods. Scand J Soc Med. 1978;6:125–9.
70. Shephard RJ, Rankinen T, Bouchard C. Test-retest errors and the apparent heterogeneity of training responses. Eur J Appl Physiol. 2004;91:199–203.
71. Skinner JS, Wilmore KM, Jaskolska A, et al. Reproducibility of maximal exercise test data in the HERITAGE Family Study. Med Sci Sports Exerc. 1999;31:1623–8.
72. Guyatt GH, Heyting A, Jaeschke R, et al. N-of-1 randomized trials for investigating new drugs. Control Clin Trials. 1990;11:88–100.
73. Lillie EO, Patay B, Diamant J, et al. The *n*-of-1 clinical trial: the ultimate strategy for individualizing medicine? Per Med. 2011;8:161–73.
74. Senn S. Suspended judgement of n-of-1 trials. Control Clin Trials. 1993;14:1–5.
75. Zucker DR, Ruthazer R, Schmid CH. Individual (n-of-1) trials can be combined to give population comparative treatment effect estimates: methodologic considerations. J Clin Epidemiol. 2010;63:1312–23.
76. Batterham AM, Hopkins WG. Making meaningful inferences about magnitudes. Int J Physiol Perform. 2006;1:50–7.
77. Hopkins WH. Precision of the estimate of a subject's true value (Excel spreadsheet). In: a new view of statistics. Internet society for sport science. 2000. www.sportsci.org/resource/stats/xprecisionsubject.xls. Accessed 21 Nov 2016.

Appendix 15 – Peer-Reviewed Paper – Inter Individual Differences in Weight Change Following Exercise Interventions: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

obesity reviews

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Physiology

Inter-individual differences in weight change following exercise interventions: a systematic review and meta-analysis of randomized controlled trials

P. J. Williamson, G. Atkinson and A. M. Batterham

Health and Social Care Institute, Teesside University, Middlesbrough, UK

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Address for correspondence: PJ Williamson, Health and Social Care Institute, Teesside University, Middlesbrough TS1 3BA, UK.
E-mail: p.williamson@tees.ac.uk

Summary

Previous reports of substantial inter-individual differences in weight change following an exercise intervention are often based solely on the observed responses in the intervention group. Therefore, we aimed to quantify the magnitude of inter-individual differences in exercise-mediated weight change. We synthesized randomized controlled trials (RCTs) of structured, supervised exercise interventions. Fourteen electronic databases were searched for relevant studies published up to March 2017. Search terms focused on structured training, RCTs and body weight. We then sifted these results for those RCTs (n = 12, 1500 participants) that included relevant comparator group data. Standard deviations (SDs) of weight change were extracted, thereby allowing the SD for true inter-individual differences in weight loss to be calculated for each study. Using a random effects meta-analysis, the pooled SD (95% CI) for true individual responses was 0.8 (−0.9 to 1.4) kg. The 95% prediction interval (based on 2SDs) for true inter-individual responses was −2.8 to 3.6 kg. The probability (% chance) that the true individual response variability would be clinically meaningful (>2.5 kg) in a future study in similar settings was 23% ('unlikely'). Therefore, we conclude that evidence is limited for the notion that there are clinically important individual differences in exercise-mediated weight change.

Keywords: Individual response variance, RCT, weight loss, treatment heterogeneity.

Introduction

Interest in the individualized response to a treatment intervention, and its applicability to medical and exercise interventions, has been growing over the last three decades (1–8). There has been specific interest in the inter-individual differences in weight change in response to exercise training for around 20 years (9–14). Such interest has developed into a dedicated field of research; precision medicine – encompassing 'tailor-made' therapies based on the individual response of a patient (5). It is predicted that this individual approach to medicine will ultimately reduce costs and improve quality of health care (15). It has also been suggested that personalized medicine may revolutionize health care through utilization of individual genetic information, thereby improving drug safety and efficacy (16). Nevertheless, associations that have been reported between genotype and treatment responses are often small (17).

A limitation of published research on the efficacy of exercise training has been reported to be the focus on group mean data, with inter-individual variation in response often being overlooked (11). Such a focus on mean effects could obfuscate important individual differences in response (11,18,19). If such individual differences are present, and predictors of individual response are identified, then

targeted intervention strategies could be formulated to maximize weight loss for individuals.

Research design and data analysis issues

There have been reports of inter-individual variation in adiposity and weight response to exercise (9–13), including observations that exercise can cause a less-than-expected weight loss for some individuals (20). It has been suggested that the response to exercise may be influenced by a multitude of individual characteristics, including sex (20,21), genetics (22), age, and baseline status of the measured outcome (23). Clinically relevant inter-individual response variation should be quantified and judged properly (24,25) before the clinical relevance of these effect modifiers of response are appraised, relative to a robust minimal clinically important difference (MCID). Crucially, this quantification requires an appropriate control/comparator group, preferably within a randomized trial design. Regrettably, substantial treatment response heterogeneity has been claimed from observations solely on the intervention group (11,13,26). When the comparator sample is absent or ignored, the interpretation of response heterogeneity is prone to all the philosophical issues highlighted by Stephen Senn, particularly the problem of the 'counterfactual' (25).

An appropriate method to quantify 'true' individual response variability in a parallel group study involves the application of the following equation; $SD_{IR} = \sqrt{SD_I^2 - SD_C^2}$ (24,27), where SD_{IR} is the true inter-individual response variability, expressed as a standard deviation, and SD_I^2 and SD_C^2 are the standard deviations of the changes in the intervention and control samples, respectively. The SD_{IR} should be interpreted as the amount by which the net mean effect of the intervention (intervention minus control) differs typically between individuals (27).

Aims of the review

In view of the design and analysis issues highlighted, there is uncertainty about previously drawn conclusions in weight-loss studies. To date, there has been no published quantitative synthesis of the evidence for individual response variation in studies on exercise-mediated weight loss. Therefore, we aimed to conduct a systematic review and meta-analysis of the available research to allow for quantification of 'true' inter-individual variation in weight change in response to an exercise intervention.

Methods

This study was undertaken in accordance with the ethics procedures and guidance of Teesside University. The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (28). The review protocol was registered with PROSPERO, the International Prospective Register of Systematic Reviews (CRD42016049982). An initial scoping literature review was undertaken to gauge the likely number of eligible studies for inclusion in the meta-analysis.

Study question

Our systematic review was designed to address the following question: Across all the relevant studies that include a suitable comparator sample, are there substantial inter-individual differences in body mass loss in response to an exercise intervention?

Literature search and study selection

This review involved a systematic electronic search of peer-reviewed original literature using the following commonly used databases: Centre for Reviews and Dissemination (York), CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstract Reviews or Effects, Database of Promoting Health Effectiveness Reviews, EMBASE, Medline (Ovid), NHS Economic Evaluation Database, PROSPERO, PubMed, SCOPUS and Sport Discus. These databases were first searched in December 2016, before a secondary search in March 2017. The search strategy was designed to include all articles published in the English language. Search terms comprised of 'exerc*' AND ('train*' OR 'condition*') AND ('structure' OR 'supervised') AND ('weight' OR 'body compos**' OR 'BMI*') AND ('randomi*' OR 'RCT'). Subsequently, additional searches of reference lists, Google Scholar and relevant bibliographic hand searches with no limit of language or publication date were also completed. Only studies conducted in humans were considered.

Studies were screened for those that would meet the inclusion criteria. Titles and abstracts were initially scrutinized to exclude those studies clearly beyond the scope of this review. For potential studies that appeared to meet the inclusion criteria, or those for which a decision was unable to be made based upon the title and abstract alone, full, published articles were obtained for detailed assessment against the inclusion criteria. Where multiple papers from a single study have been published, these were treated as a single study. Included studies were randomized intervention studies, reporting the standard deviation of the change in body mass in both arms. All studies targeting specific populations (e.g. pregnant women, children and individuals suffering from specific diseases) were excluded. The remaining full-text articles were included in the systematic review and meta-analysis. A complete overview of the process is

presented at Fig. 1, and a comprehensive summary of the studies reviewed is presented in Table 1.

Two reviewers (PW and GA) independently assessed publications for eligibility. The decision to include studies was hierarchical and made initially upon the basis of the study title, abstract and presence of keywords. When a study could not be excluded with certainty, the full text was obtained for evaluation. Disagreements between reviewers were resolved through discussion with a third reviewer (AB), and a consensus approach was used.

Study eligibility

Inclusion criteria

To be included for quantitative synthesis, studies were required to meet the following criteria: (1) participants were required to be aged 18 or over; (2) taking part in studies where the experimental arm was an exercise-based intervention; (3) which was designed to elicit weight loss; (4) reporting change in adiposity indices (body mass index, body fat or body weight); (5) with no history of diabetes, metabolic, cardiovascular, musculoskeletal or inflammatory disease; (6) the exercise intervention was required to be supervised; (7) the investigation had to be an RCT design; and (8) greater than 6 weeks in duration. Because the interventions were exercised-based, investigators and participants were not blinded. Studies were included if they were published in peer-reviewed journals or full manuscripts were available (i.e. theses and dissertations). Where several intervention arms were present, all data other than that from the control-only and exercise-only arms were excluded. Where more than one exercise intervention was present, results were combined to avoid double counting of the control sample (29). The same procedure for combining groups was applied to studies with a single exercise intervention but with results reported separately for sub-groups.

Exclusion criteria

Studies were excluded if they (1) included unsupervised exercise interventions, behaviour therapy, dietary modification, health education, surgical and drug or hormone treatment that did not include exercise; (2) if change in body mass/composition was not a primary or secondary aim of the study; (3) if no relevant comparator sample was present; or (4) the full-text manuscript was written in a language other than English.

Data extraction and synthesis

DigitizeIt (Brunschweig, Germany) graph digitizer software was used in cases where data were only presented in figures rather than text or tables.

Study characteristics such as study design, participant characteristics (age, sex and ethnicity), measurement methods, change scores, SD_{change} and information to assess the risk of bias were extracted by the lead author.

A standardized data extraction sheet was used to collect data on participants' characteristics, study methods, sample size, prescribed intervention (frequency, intensity, duration and type), outcomes assessed, loss to follow-up and study type. The data for Table 1 and Fig. 1 were collected by PW before GA verified its accuracy and the eligibility of studies for inclusion. Where data were incompletely or unclearly reported, the lead author contacted study authors for clarification. Effect sizes were calculated for the relevant measures.

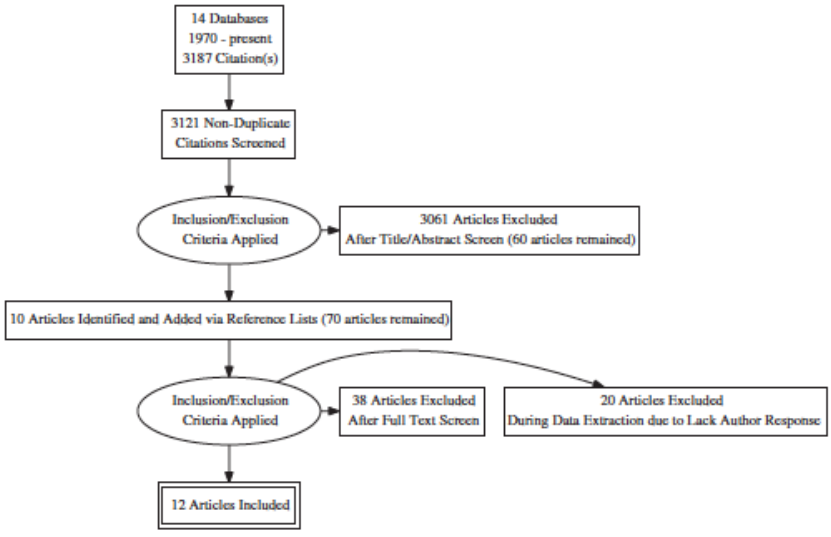

Figure 1 Flow diagram of the systematic review process.

Table 1 Studies presenting weight loss response to supervised exercise interventions

Literature citation	Subjects/ groups	Exercise training programme			Results	
		Mode	Length	Intensity/frequency/duration/ volume	Δ BW (kg) ± SD	Other
Baillot *et al.*, 2016 (66)	*n* = 15 (EX), *n* = 14 (CON)	Endurance and circuit style with nine stations	12 weeks	3 per week, 80 min–10WU, 50–60 MB (30-min endurance, including treadmill, elliptical, arm ergo cycle, 20 to 30-min strength), 10CD. Endurance at 55–85% HRR	EX −0.92 (3.55), CON −0.3 (4.72)	Pre-Surgical Exercise Training (PreSET) intervention also improved social interaction and PA barriers
Burtscher *et al.*, 2009 (64)	*n* = 18 (EX), *n* = 18 (CON)	Aerobic training and circuit training	12 months	2 per week, 60 min, aerobic exercise (dancing, walking, running, skating and swimming) eliciting lactate response of 2–3 mmol/L, interspersed with higher intensity efforts. Circuits included 6–8 exercises, 8–12 reps. All participants also advised to exercise for 30 min/d	EX −2.58 (4.12), CON 0.79 (4.93)	Counselling and supervised exercise maintained exercise capacity versus counselling alone. In EX, dietary goals (<BW by 5%) not achieved
Church *et al.*, 2009 (56)	*n* = 317 (EX), *n* = 94 (CON)	Aerobic training alternating treadmill and cycle ergometer	26 weeks	3–4 per week, CON +3 EX groups – 4, 8 and 12 Kcal/kg BW, 50% VO_2 alternating between semi-recumbent cycling and treadmills	EX −4 Kcal −1.4 (3.6), 8 Kcal −2.1 (3.5), 12 Kcal −1.5 (3.4) combined intervention −1.62 (3.5), CON −0.9 (3.37)	No difference between predicted and actual weight loss at 4 and 8 Kcal/kg, 12 Kcal/kg lost only half predicted amount
Dalager *et al.*, 2016 (67)	*n* = 89 (EX), *n* = 195 (CON)	Aerobic and resistance training	1 year	1 per week, 20-min aerobic exercise (running, rowing and ball games) 77–95% HR_{max}, 30-min resistance training 60–80% 1RM for three sets of eight reps, recommendations to undertake 30-min exercise per day at 64–76% HR_{max}	EX −0.49 (3.32), CON 0.08 (2.97)	5% (ITT) and 10% (PPA) > Δ VO_2max in EX than INT, 2.8% ∇in SBP
Donges *et al.*, 2010 (62)	*n* = 76 (EX), *n* = 26 (CON)	Aerobic and resistance training	10 weeks	RT 30–50 min, 2–4 sets of 8–10 reps @ 70–75% of 10RM, AT 30 to 50-min cycle ergometer 70–75% MHR	RT 0.8 (1.5), AT −0.8 (1.9), combined −0.06 (1.89) CON 0.6 (1.3)	AT >Δ in body composition than RT and CON. CRP reduced in RT, IL6 unchanged in all groups
Donnelly *et al.*, 2013 (58)	*n* = 74 (EX), *n* = 18 (CON)	Aerobic training	10 months	5 per week, aerobic exercise – walking/jogging on treadmill (20% of sessions were undertaken on alternative activities such as stationary cycling, elliptical or walking/jogging outside), expending 400 and 600 Kcal/session	400 Kcal −3.9 (4.9), 600 Kcal −5.2 (5.6), combined EX −4.55 (5.27), CON 0.5 (3.5)	No significant difference between exercise intervention, suggested some compensatory mechanisms, or when stratified by gender
Lockwood *et al.*, 2008 (63)	*n* = 14 (EX), *n* = 10 (CON)	Aerobic and resistance training	10 weeks	AT 3 per week, self-selected exercise 15–35 min @ 40–70% HRR, RT 2 per week, 1 set of 8–12 reps (or to failure)	EX −0.3 (1.87), CON −0.3 (1.58)	Individual variation in *ad libitum* EI reported to be linked with compensatory EI in EX
Prabhakaran *et al.*, 1999 (59)	*n* = 12 (EX), *n* = 12 (CON)	Resistance training	14 weeks	3 per week, 45–50 min/session, 85% 1RM, loading major muscle groups, 2 sets of 8 reps plus 1 set to failure, 30 to 60-s rest	EX −0.7 (1.35), CON 0.49 (2.01)	Reduction in lipids and body fat % in EX
Schmitz *et al.*, 2002 (60)	*n* = 27 (EX), *n* = 27 (CON)	Resistance training	15 weeks	2 per week, 50 min, 3 sets of 8–10 reps, 9 exercises	EX 0.54 (1.87), CON 0.49 (1.82)	Strength training produced favourable Δ in fasting glucose, insulin and cancer risk factors

(*Continues*)

Table 1 (Continued)

Literature citation	Subjects/ groups	Exercise training programme			Results	
		Mode	Length	Intensity/frequency/duration/ volume	Δ BW (kg) ± SD	Other
Tan *et al.*, 2012 (57)	*n* = 29 (EX), *n* = 19 (CON)	Track running	8 weeks	5 per week, 40 min of running at individualized Fat_{max} HR on outdoor track	EX −4.1 (1.6), CON 0.3 (1.2)	Fat_{max} also decreased fat mass, waist-hip ratio (both possibly related to change in fat oxidation rates), fasting plasma concentration (increased use of fat as fuel) and increased VO_2max
Teixeira *et al.*, 2003 (61)	*n* = 117 (EX), *n* = 116 (CON)	RT, circuit and weight bearing aerobic exercise	12 months	3 per week, RT 60–70 min, 2 sets of 6–8 reps at 70–80% 1RM, AT included walking, jogging, skipping and hopping, 10 min as WU, then 20–25 min @ 60% HR_{max}	EX (with HRT/without HRT) −0.2 (2.6)/0.34 (2.5) combined SD 2.55, CON (with HRT/ without HRT) 0.8 (2.7)/−0.4 (3.3), combined SD 3.05. Total EX 0.07 (2.55), CON 0.23 (3.05)	Δ LST in all who exercised and non-exercisers not taking HRT, decreased FT on women on HRT. HRT appeared to protect against loss of LST
Vilela *et al.*, 2015 (65)	*n* = 30 (EX), *n* = 30 (CON)	RT, sporting activity	4 months	5 per week, RT including 2-d upper body exercises and 2-d lower body exercises. 4 × 10-min 3 sets of 30-s work, 30-s recovery, 5-min flexibility, 1 × 15-min sporting activity (soccer, volleyball and basketball)	EX 0.0 (2.6), CON 0.4 (2.6)	EX reduced body fat by 4.8 (1.8) %, in the absence of weight loss, suggesting increased lean tissue

AT, aerobic training; BW, body weight; CD, cool-down; CON, control condition; CRP, C-reactive protein; EI, energy intake; EX, exercise condition; Fat_{max}, intensity of maximal fat oxidation; FT, fat tissue; HR_{max}, maximal heart rate; HRR, heart rate reserve; HRT, hormone replacement therapy; IL6, interleukin 6; ITT, intention to treat; Kcal, Kilocalorie; kg, kilograms; LST, lean soft tissue; MB, main body of exercise session; min, minutes; mmol/L, millimole per litre; PA, physical activity; PPA, per protocol analysis; Reps, repetitions; RM, repetition maximum; RT, resistance training; s, seconds; SBP, systolic blood pressure; SD, standard deviation; VO_2, oxygen uptake; VO_{2max}, maximal oxygen uptake; WU, warm-up.

Assessment of study quality

Methodological risk of bias was assessed and reported in accordance with the Cochrane Handbook (29) and the guidelines of the Cochrane Consumers and Communication Review Group (30), which recommend the explicit reporting of the following elements for RCTs: random sequence generation, allocation sequence concealment, blinding (participants and personnel), blinding (outcome assessment), completeness of outcome data, selective reporting and other sources of bias. Each item was judged as being at high, low or unclear risk of bias as set out in the criteria provided (29). A summary of risk of bias is presented in Figs 2 and 3, produced by using RevMan software (Review Manager. Version 5.3. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2014).

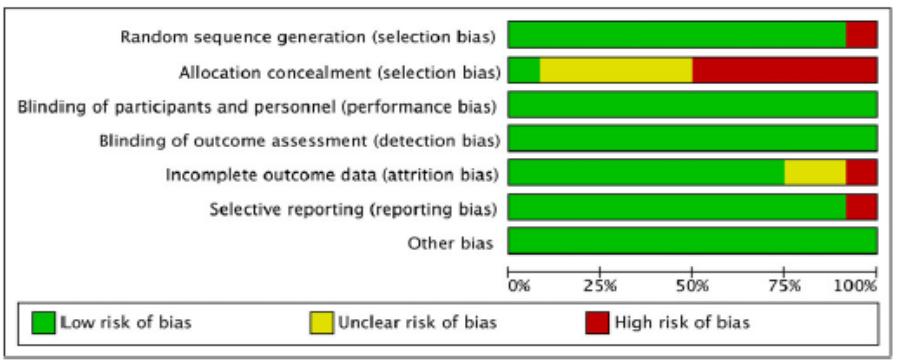

Figure 2 Risk of bias graph.

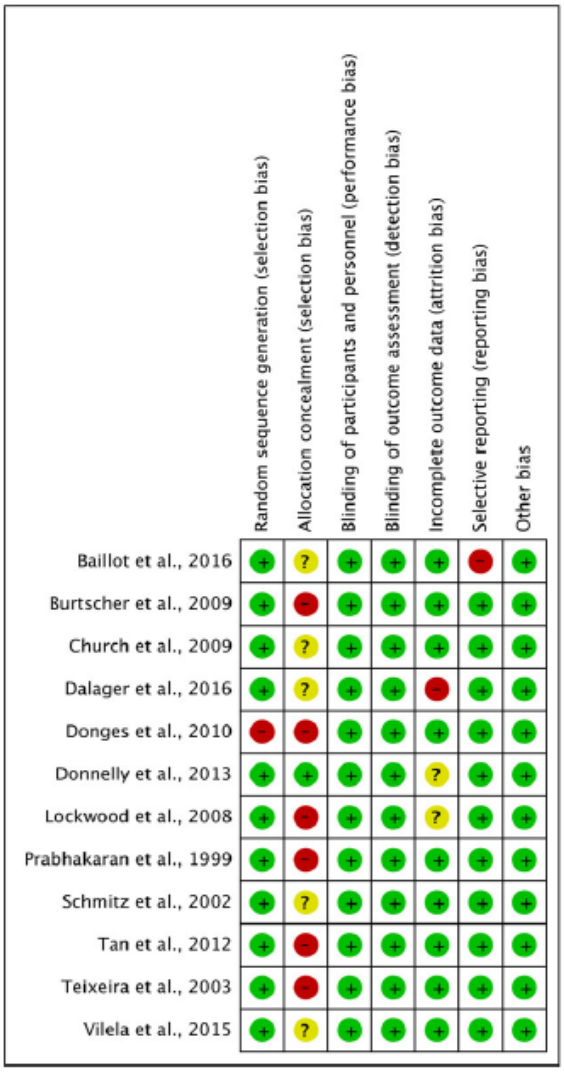

Figure 3 Risk of bias summary.

Studies were deemed to be at highest risk of bias if they scored as high or unclear risk of bias for either the sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias (29).

In all cases, risk of bias was independently assessed (by PW and GA), with any disagreements resolved by discussion to reach consensus. Risk of bias results were incorporated into the review by using standard tables, systematic narrative discussion and commentary about each element, leading to an overall assessment of the risk of bias of those studies selected for inclusion and a judgement about the internal validity of the review's results.

Meta-analysis

First, to put the results for individual response variance in context, we conducted a random-effects meta-analysis for the mean difference in weight loss across the included studies, using a restricted maximum likelihood (REML) model combined with the Knapp-Hartung method (*t*-distribution for between-study variance). Second, for each study, we extracted the standard deviation of the changes in body mass for both control (C) and exercise intervention (I) groups. The true individual response variance (intervention minus control) was then derived as $SD_I^2 - SD_C^2$. The standard error (SE) for this variance was calculated by using the following equation:

$SE = \sqrt{[2(SD_{Exp}^4/DF_{Exp} + SD_{Con}^4/DF_{Con})]}$, where DF_{Exp} and DF_{Con} are the degrees of freedom of the standard deviations in the exercise and control groups (28). Note that a negative value for the individual response variance, for either the point estimate or lower bound of the confidence interval (CI) or prediction interval, implies greater variability in the changes in body mass in the control versus intervention groups.

The individual response variances with their SEs were meta-analysed by using an REML model combined with the Knapp-Hartung method. It is important to note that the variances are unbiased, whereas the SD is not, and deriving an SE for the SD for individual responses is also problematic. Therefore, synthesizing the individual response variances rather than the SDs for individual responses is imperative. We derived the point estimate for the pooled individual response variance together with its uncertainty expressed as a 95% CI. The point estimate and confidence limits were then converted to an SD metric by taking the square root. In the case that the lower limit of the interval was negative, we first ignored the sign, took the square root, and then re-applied the sign. This approach is consistent with the 'no bound' option in SAS/STAT® software, which permits negative variances (SAS Institute Inc. 2017. SAS/STAT 14.3 User's Guide. Cary, NC: SAS Institute Inc.).

For both meta-analyses, between-study heterogeneity was quantified through the tau statistic (τ) – an SD describing the typical variability in the mean effect between studies (31). Using the SE for the pooled mean effect and the tau, a 95% prediction interval was derived to quantify the expected range of true effects in future studies in similar settings (32). For the individual response variability, this prediction interval was derived for $2 \times SD_{IR}$, as the SD_{IR} should be doubled before evaluating its magnitude to reflect a comparison between a typically high (mean + SD_{IR}) and typically low (mean − SD_{IR}) responder (27). The magnitude of both the mean weight loss and the individual response variability ($2 \times SD_{IR}$) was evaluated against a minimum clinically important difference for weight loss of 2.5 kg (33) by calculating the probability that the effect in a future study in similar settings would exceed this threshold (32). This probability was interpreted by using the

qualitative probabilistic anchors advanced by Hopkins *et al.* (34). Inasmuch as we must work with the response variances, rather than the SDs, we first halved the MCID (equivalent to doubling the SD for individual responses), squared it (to express it in variance metric), and then derived the probability that the response variance in a new study would be clinically relevant, as described in the preceding texts. The threshold of 2.5 kg for the minimum clinically important weight loss was chosen, conservatively, as the lowest value from the range of clinically relevant effects presented by Jensen *et al.* (33). By definition, effects smaller than this threshold are defined as trivial (not clinically relevant). Effects >2.5 kg but <7.5 kg are defined as 'small' (yet clinically important). We define 'moderate' effects as >7.5 kg but <15 kg and 'large' effects as >15 kg (34).

All statistical analyses were conducted by using Comprehensive Meta-Analysis software, version 3 (Biostat Inc., Englewood, NJ, USA).

Results

Study selection

The initial search generated 3187 results (Fig. 1). Three thousand sixty-one of these were excluded based on titles and abstracts alone, and 66 duplicates were rejected. The complete text was obtained for 60 articles. A further 10 were identified from relevant reference lists and hand searches. Following examination of these articles, 12 were identified that met the eligibility criteria and are summarized in Table 1. A further 20 met all selection criteria, apart from the reporting of SD_{change}. The authors of these papers were contacted, but only four responses were received, and full data were not provided in these instances (35–54). Contact was made by email. If, after 4 weeks, no response was received, a further email was sent. Following a further 4-week period, papers from these authors were excluded. One paper met all inclusion criteria (55), except for the fact that median and interquartile range values were presented for changes in body mass, rather than means and SDs. No non-published studies (i.e. dissertations) were found to be eligible for inclusion.

The included studies encompassed a 17-year publication period between 1999 and 2016. Included studies involved a total of 1500 participants (EX: n = 922, CON: n = 578). Three trials involved outcomes of aerobic training interventions (56–58), three involved the outcomes of resistance training interventions (59–61), one study involved the outcomes on separate aerobic and resistance training interventions (62), and five studies involved the outcomes of combined/concurrent training (63–67). The duration of studies ranged from 8 to 52 weeks, study sample sizes ranged from 24 to 411, and reported pre-intervention mean body mass ranged from 65.5 to 128.0 kg.

Study outcomes

The pooled mean group difference in pre/post changes in weight (intervention minus control) was −1.4 kg (95% CI −0.3 to −2.5 kg). Substantial between study heterogeneity was observed (τ = 1.5 kg: −0.4 to 2.2 kg). The prediction interval revealed that, were investigators to undertake a future trial, the 95% plausible range for mean weight change versus control would be −5.0 to 2.1 kg. The probability (% chances) that the mean weight loss (intervention minus control) in a future study in similar settings would exceed the minimum clinically important difference of a reduction of 2.5 kg was 26% ('possibly' clinically important).

The pooled point estimate for the inter-individual variability in weight change in response to an exercise intervention (SD_{IR}) was 0.8 (−0.9 to 1.4) kg. The between-study heterogeneity (τ) was 1.0 (−1.7 to 2.2) kg. The 95% prediction interval for 2 × SD for true inter-individual responses was −2.8 to 3.6 kg. The probability (% chances) that the individual response variability (2 × SD) in a future study in similar settings would be clinically meaningful (>2.5 kg) is 23% – 'unlikely' to be clinically important. Therefore, the odds are greater than 3:1 against the notion that there is clinically relevant individual response variance.

Study quality and risk of bias

Table 2 and Figs 2 and 3 present a summary of risk of bias within included studies. Overall, risk of bias was mostly low or of unclear risk in the outcome of interest.

Discussion

The aim of our review was to synthesize the available evidence for inter-individual variation in weight change following an exercise-focussed intervention. This is the first systematic review and meta-analysis designed to address this specific aim. We found that the evidence is limited for clinically relevant 'true' inter-individual variation in weight change in response to an exercise intervention, once the random variability in weight over time in the control group is accounted for. Also, the observed pooled inter-individual response variability, when compared with the pooled mean change in weight, was small. The prediction interval ranged from small negative (more response variability in control group) to small positive (more variability in the exercise arm), and revealed that the magnitude of the true individual response variability in a future study in similar settings is unlikely to be clinically important. Similarly, the prediction interval for the mean weight loss ranged from moderate reduction to trivial weight gain and indicated that the magnitude of mean weight loss in a future study in similar settings was only possibly clinically relevant.

Table 2 Summary descriptives of risk of bias for each of the included studies, in accordance with Cochrane guidelines (29).

Literature citation	Random sequence generation		Allocation concealment		Blinding of participants		Blinding of outcome assessment		Incomplete outcome data addressed		Selective reporting		Other	
	Risk		Risk		Risk		Risk		Risk		Risk		Risk	Comment
Baillot *et al.*, 2016 (66)	Low	Quote 'Patients were randomly allocated'. Comment: Likely done	Unclear	Quote 'Allocation was generated by a computer random sequence and kept in sealed envelopes'. Comment: Likely done	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes.	Low	Quote: 'The only subject who abandoned the research project was in the usual care group and excluded from analyses'. Comment: Likely done	High	Six domains for WRQL in methods, only one reported in written format; others presented in table format	Low	The study appears free from other sources of bias.
Burtscher *et al.*, 2009 (64)	Low	Quote 'Patients were randomly assigned'. Comment: Likely done	High	Comment: 'No information provided on method of randomization'. Comment: Possibly not done	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes.	Low	Quote: 'Due to financial problems, we had to terminate the exercise programme at Month 12. To minimize possible bias, 18 patients were then compared with age- and gender-matched patients in a nested cohort approach'. Comment: Likely done	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way	Low	The study appears free from other sources of bias.
Church *et al.*, 2009 (56)	Low	Quote 'Patients were randomized to 1 of 3 exercise groups or a non-exercise control'. Comment: Likely done	Unclear	Quote 'The randomization sequence is computer generated by the study statistician'. Comment: Statement found in published rationale paper. Possibly done	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes.	Low	Comment: Missing data relatively balanced across intervention groups. Additionally, missing data were imputed by carrying forward from previous observation (1 week).	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way	Low	The study appears free from other sources of bias.
	Low	Quote 'Office workers were	Unclear	Quote: 'The participants	Low	Comment: Exercise	Low	Quote: 'The study was a 2-year, parallel	High	Quote: 'Missing values in either baseline or	Low	Comment: Study	Low	The study

(*Continues*)

Table 2 (Continued)

Literature citation	Random sequence generation		Allocation concealment		Blinding of participants		Blinding of outcome assessment		Incomplete outcome data addressed		Selective reporting		Other	
	Risk		Risk		Risk		Risk		Risk		Risk		Risk	Comment
Dalager *et al.*, 2016 (67)		randomized 1:1 to a training group or a control group'. Comment: Likely done		were assigned with an arbitrary ID number and randomized individually, using a random number computer algorithm'. Comment: Possibly done		interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.		group, examiner blinded RCT'. Comment: Likely done		follow-up measurement were substituted with data carried forwards or backwards'. Comment: Missing data unbalanced across intervention groups. It is unknown as to what impact this might have on effect sizes.		protocol available and all pre-specified outcomes reported in pre-specified way		appears free from other sources of bias.
Donges *et al.*, 2010 (62)	High	Quote 'Participants were semi randomly assigned….80% were randomly assigned, however 20% were allocated according to matching or preference'.	High	Comment: No information provided on method of randomization, other than describing it as 'semi-random'	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes.	Low	Comment: No missing data apparent	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way	Low	The study appears free from other sources of bias.
Donnelly *et al.*, 2013 (58)	Low	Quote: 'Participants were randomized (2:2:1) to exercise or non-exercise'. Comment: Likely done	Low	Quote: 'Participants were stratified by gender and randomized by an independent statistician'. Comment: Possibly done	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Quote: 'Investigators and research assistants were blinded at the level of outcome assessments'. Comment: Likely done	Unclear	Comment: No methodology for approaching massing data. Missing data relatively balanced across intervention groups	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way	Low	The study appears free from other sources of bias.
Lockwood *et al.*, 2008 (63)	Low	Quote: 'Subjects were randomly assigned'.	High	Comment: No information provided on	Low	Comment: Exercise interventions preclude the	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would	Unclear	Comment: No methodology for approaching missing data. Missing data	Low	Comment: Study protocol available	Low	The study appears free from

(*Continues*)

Table 2 (Continued)

Literature citation	Random sequence generation		Allocation concealment		Blinding of participants		Blinding of outcome assessment		Incomplete outcome data addressed		Selective reporting		Other	
	Risk		Risk		Risk		Risk		Risk		Risk		Risk	Comment
		Comment: Likely done		method of concealment		blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.		not influence outcomes.		relatively balanced across intervention groups		and all pre-specified outcomes reported in pre-specified way		other sources of bias.
Prabhakaran *et al.*, 1999 (59)	Low	Quote: 'Subjects were randomly assigned to either a non-exercising control group or a resistance exercise training group'. Comment: Likely done	High	Comment: No information provided on method of concealment	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes.	Low	Comment: Missing data relatively balanced across intervention groups	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way	Low	The study appears free from other sources of bias.
Schmitz *et al.*, 2002 (60)	Low	Quote: 'Randomized to no-contact control or treatment'. Comment: Likely done	Unclear	Comment: Randomization stratified by decade (30–39), (40–50) due to concerns regarding effects of hormonal changes	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Quote: 'Body weight and height measurements, blood draws and DEXA (body composition) were performed by clinical research nurses, blinded to treatment groups'. Comment: Likely done.	Low	Comment: Missing data relatively balanced across intervention groups	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way	Low	The study appears free from other sources of bias.
Tan *et al.*, 2012 (57)	Low	Quote: 'Participants were randomly allocated into two groups'. Comment: Likely done	High	Comment: No information provided on method of randomization	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes.	Low	Comment: Missing data relatively balanced across intervention groups. Additionally, reasons unlikely to affect outcome measures	Low	Comment: Study protocol available and all pre-specified outcomes reported in	Low	The study appears free from other sources of bias.

(*Continues*)

Table 2 (Continued)

Literature citation	Random sequence generation		Allocation concealment		Blinding of participants		Blinding of outcome assessment		Incomplete outcome data addressed		Selective reporting		Other	
	Risk		Risk		Risk		Risk		Risk		Risk		Risk	Comment
						is judged that this would not influence outcomes.						pre-specified way		
Teixeira *et al.*, 2003 (61)	Low	Quote: 'Subjects were randomly allocated to assigned to one year of weight-lifting and weight-bearing exercise or to a group with no exercise'. Comment: Likely done	High	Comment: Subjects stratified by HRT status	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Quote: 'DEXA technicians were blind to participants group assignments'. Comment: Likely done	Low	Comment: No missing data apparent	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way	Low	The study appears free from other sources of bias.
Vilela *et al.*, 2015 (65)	Low	Quote: 'Randomly distributed in control and experimental groups'. Comment: Likely done	Unclear	Quote: 'Randomly assigned drawing an opaque envelope', with 'names written on them'. Comment: Likely done	Low	Comment: Exercise interventions preclude the blinding of participants to allocated group during the study. It is judged that this would not influence outcomes.	Low	Comment: No mention of blinding of outcome assessment. It is judged that this would not influence outcomes.	Low	Comment: No missing data apparent	Low	Comment: Study protocol available and all pre-specified outcomes reported in pre-specified way	Low	The study appears free from other sources of bias.

If study methodology did not explicitly state allocation was randomized, then it was deemed 'high risk' of bias for allocation concealment. Only those studies using central randomization, sequentially numbered drug containers or sequentially numbered, opaque, sealed envelopes were deemed 'low risk'.

Aerobic training interventions

Aerobic training has been reported to provide positive changes in body mass and body composition (68,69). In the current review, three studies were designed to investigate the effect of aerobic training interventions on weight loss, amongst other outcomes (56–58). Although all three studies showed greater variability of changes in weight in the intervention arm, only one showed substantial 'true' individual response variability. As part of the large-scale Mid-West Exercise Trial 2, a control sample (n = 18) was compared with groups engaging in 5 d per week of aerobic exercise eliciting 400 Kcal (n = 37) and 600 Kcal (n = 37) of energy expenditure per session (58). Whilst group means evidenced substantial changes in body weight (400 Kcal: −3.9 kg, 600 Kcal: −5.2 kg, control: 0.5 kg), greater variability of changes (SD) was observed in the two intervention groups (400 Kcal: 4.9 kg, 600 Kcal: 5.6 kg, pooled SD: 5.27 kg) than in the control sample (3.5 kg). The SD for individual response for this study was therefore 3.9 kg (95% CI, 1.8 to 5.3 kg). The individual response variability in this study is clearly clinically relevant: 2 × SD for individual response > MCID for the lower confidence limit. Indeed, the true individual response variance in this study was at least seven-fold greater than any other included study. Nevertheless, removal of this study from the meta-analysis had no material effect on the pooled SD for inter-individual variation in response (0.7 kg, versus 0.8 kg with all studies included) and a negligible effect on the heterogeneity. This finding is due in part to the low weight afforded to this study in the analysis – just 1.03% - primarily due to relatively small sample size.

Resistance training interventions

Three of the included papers were designed to investigate the effects of resistance training on body weight (59–61). Of these, one study showed a larger SD of body mass changes over 15 weeks of resistance training in intervention versus control (60). This study reported trivial increases in mean body mass in both groups (EX: 0.54 kg, CON: 0.49 kg). The SD of the changes was 1.87 kg in intervention versus 1.82 in control, resulting in a trivial SD for individual response of 0.4 kg.

Separate aerobic and resistance training interventions

A single paper reported upon the impact of separate training modalities (62). The SD of the change in body mass was 1.3 kg in control, 1.5 kg in resistance training, and 1.9 kg in aerobic training (pooled intervention SD of changes = 1.89 kg). The SD for individual response in this study was therefore 1.4 kg, representing small individual response variability.

Combined/concurrent training

The effects of concurrent training on body composition are equivocal. Weight loss (70) and weight gain (68) have been reported, but other health outcomes are often also positively influenced (71). Five studies included in the present review were designed to examine the effects of combined or concurrent aerobic and resistance exercise protocols (63–67). Clinically relevant individual response variability was present in just one trial of an intervention involving 12 months of 1 h per week combined aerobic and circuit-style training (n = 193), alongside recommendations to undertake 30 min of exercise, 6 d per week, compared with a non-exercise control group (n = 194) (67). Mean weight change was −0.49 kg in the intervention group versus 0.08 kg in control, with SD of the changes of 3.32 and 2.97 kg, respectively. The SD for individual response was therefore 1.5 kg.

Limitations

We synthesized 12 studies involving a total of 1500 participants. Small sample size is common in supervised exercise-based intervention trials (72), but our review included four larger (n= > 100) studies (56,61,62,67). Six studies recruited fewer than 20 participants for one or more of the groups (57–59,63,64,66) and might be prone to small study bias at the individual study level.

We restricted our search to RCTs incorporating exercise-only interventions; included studies differed by exercise mode, intensity, frequency and duration, and length of intervention. This intervention heterogeneity might influence mean effects and/or individual response variance. There are too few studies to compare the effects in, for example, aerobic versus resistance versus combined interventions.

Given the substantial heterogeneity of the true individual response variance, we derived and presented a prediction interval capturing the plausible range for the true individual response variability, consistent with the data and model, in a future study in similar settings. The prediction interval has been described as providing "potentially the most relevant and complete statistical inferences to be drawn from random effects meta-analyses" (73). However, we exercise due caution in inferences drawn from the prediction interval given the coverage issues identified in the simulations conducted by Partlett and Riley (74). These authors reported that the coverage of the interval was particularly poor in cases of low effect heterogeneity and/or markedly variable sample size. With the specific combination of number of studies, between-study heterogeneity of individual response

variance and mixture of study sizes in the current review (with REML and Knapp-Hartung estimation), these simulations indicate a maximum under-coverage of our derived prediction interval of 1%. Such under-coverage would have no material effect on the derived probability of individual response variance in a future trial being clinically relevant. However, we still consider it prudent to view our prediction interval as approximate, as recommended by Partlett and Riley (74).

Where multiple exercise arms were present in a study, these were combined to avoid double counting of the control arm. This may obscure the effect of different exercise doses; however, analysis of each individual exercise condition versus control revealed no material difference in individual response variability.

In advance of the study, we proposed various potential effect modifiers (moderators) to account for heterogeneity in individual response variance, including baseline body weight, age and sex. However, we elected not to conduct any secondary meta-regression analyses, as we only had access to study-level covariates (e.g. mean baseline weight, mean age and proportion of men/women). Fisher *et al.* (75) describe this type of analysis as 'daft', as it has a high risk of ecological bias (76); the 'deft' approach advocated by Fisher *et al.* (75) requires either study level analysis of the effects of putative effect modifiers (e.g. treatment interaction effects with sex, age and weight) or an individual-participant data meta-analysis, with relevant interaction terms included in the model. However, obtaining individual participant data from study authors would likely prove to be a major undertaking in this, or indeed any, review. This contention is underscored by the difficulties we experienced in communicating with authors merely to obtain a simple standard deviation of change scores from the data.

Additionally, the energy expenditure induced by the exercise interventions undertaken in the included studies – and whether this would be sufficient, in theory, to induce weight loss above the MCID – is unknown. Whilst beyond the scope of this systematic review and meta-analysis, it is therefore unknown what effects exercise protocols with larger energy expenditures would elicit.

To make inferences in the current study, we adopted a threshold for the minimum clinically important weight loss of 2.5 kg – the smallest threshold of absolute weight loss for clinical benefit reported by Jensen *et al.* (33). Readers who disagree with this choice may consider our reported prediction intervals in relation to their own belief in the minimum clinically important difference to make inferences.

Finally, we acknowledge that 20 possibly eligible studies were excluded due to their authors not providing the data requested by email communication. We assume that these studies are missing at random, as we have no reason to believe that the authors would withhold data pertaining to response variance.

Findings in relation to current recommendations and future research directions

This is the first systematic review to focus on the true inter-individual variation in weight loss in response to exercise interventions. We conducted a comprehensive literature search over 14 databases. Evidence in relation to the inter-individual response to various treatments/interventions is growing rapidly. However, based on the findings of this systematic review, we find limited evidence for the presence of clinically important 'true' inter-individual variation in body mass in response to exercise training. Therefore, further investigation of underpinning mechanisms is likely not warranted, as the prediction interval reveals that individual response variance in a future study in similar settings is unlikely to be clinically important. A caveat here, as acknowledged in the preceding text, is that we only synthesized 12 effects from heterogeneous exercise interventions. If individual differences in response to interventions targeting body weight are considered important from a precision medicine standpoint, then future randomized trials should be sufficiently sized to afford adequate precision of estimation for both mean intervention effects and the SD for individual responses. The latter would require at least 4× the sample size required to define the mean intervention effect with adequate power and precision, and even larger samples if individual response variance is trivial-small.

Conclusions

To date, much of the research claiming to evidence substantial inter-individual differences in response to an exercise intervention has been conducted in the absence of a suitable comparator sample (11,13,14). To quantify the true inter-individual response to an exercise intervention, studies should include a comparator arm, preferably in a randomized controlled trial. Future work should employ this research design, and incorporate sound statistical quantification of the response variance in each arm, combined with a threshold for the MCID, to determine the presence of clinically important individual variation in response. In summary, our findings constitute limited evidence for the notion of substantial inter-individual differences in weight loss responses to exercise interventions; individual response variability in a future trial in similar settings is unlikely to be clinically important. Our findings, if replicated, confirmed and extended, might prevent researchers wasting valuable resources searching for explanations of treatment heterogeneity that does not exist or is clinically trivial.

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Conflict of interest statement

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References

1. Prud'Homme D, Bouchard C, LeBlanc C, Landry F, Fontaine E. Sensitivity of maximal aerobic power to training is genotype-dependent. *Med Sci Sports Exerc* 1984; **16**: 89–93.
2. Lortie G, Simoneau JA, Hamel P, Boulay MR, Landry F, Bouchard C. Responses of maximal aerobic power and capacity to aerobic training. *Int J Sports Med* 1984; **5**: 232–236.
3. Hamel P, Simoneau J, Lortie G, Boulay MR, Bouchard C. Heredity and muscle adaptation to endurance training. *Med Sci Sports Exerc* 1986; **18**: 690–696.
4. Rose EA, Partfitt G. A quantitative and qualitative explanation of the individual differences in affective responses to prescribed and self-selected exercise intensities. *J Sport Exerc Psychol* 2007; **29**: 281–309.
5. Senn S, Rolfe K, Julious SA. Investigating variability in patient response to treatment—a case study from a replicate cross-over study. *Stat Methods Med Res* 2011; **20**: 657–666.
6. Bouchard C. Genomic predictors of trainability. *Exp Physiol* 2012; **97**: 347–352.
7. Bouchard C, Antunbes-Correa LM, Ashley EA *et al.* Personalized preventive medicine: genetics and the response to regular exercise in preventive interventions. *Prog Cardiovasc Dis* 2014; **57**: 337–346.
8. Mann TN, Lamberts RP, Lambert MI. High responders and low responders: factors associated with individual variation in response to standardized training. *Sports Med* 2014; **44**: 1113–1124.
9. Snyder KA, Donnelly JE, Jabobsen DJ, Hertner G, Jakicic JM. The effects of long-term, moderate intensity, intermittent exercise on aerobic capacity, body composition, blood lipids, insulin and glucose in overweight females. *Int J Obes (Lond)* 1997; **21**: 1180–1189.
10. Barbeau P, Gutin B, Litaker M, Owens S, Riggs S, Okuyama T. Correlates of individual differences in body-composition changes resulting from physical training in obese children. *Am J Clin Nutr* 1999; **69**: 705–711.
11. King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE. Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss. *Int J Obes (Lond)* 2008; **32**: 177–184.
12. Barwell ND, Malkova D, Leggate M, Gill JM. Individual responsiveness to exercise-induced fat loss is associated with change in resting substrate utilization. *Metabolism* 2009; **58**: 1320–1328.
13. Caudwell P, Hopkins M, King NA, Stubbs RJ, Blundell JE. Exercise alone is not enough: weight loss also needs a healthy (Mediterranean) diet? *Public Health Nutr* 2009; **12**: 1663–1666.
14. Caudwell P, Gibbons C, Hopkins M, King N, Finlayson G, Jl B. No sex difference in body fat in response to supervised and measured exercise. *Med Sci Sports Exerc* 2013; **45**: 351–358.
15. Spear BB, Heath-Chiozzi M, Huff J. Clinical applications of pharmacogenetics. *Trends Mol Med* 2001; **7**: 201–204.
16. Katsanis SH, Javitt G, Hudson KA. case study of personalized medicine. *Science* 2008; **320**: 53–55.
17. Khoury MJ, Galea S. Will precision medicine improve population health? *JAMA* 2016; **316**: 1357–1358.
18. Bouchard C. Human adaptability may have a genetic basis. In: Landry F (ed.). Health and Risk Estimation, Risk Reduction and Health Promotion, Proceedings of the 18th annual meeting of the society of prospective medicine. Canadian Public Health Association: Ottawa, 1983, pp. 463–476.
19. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc* 2001; **33**(S6): S452–S453.
20. Donnelly JE, Smith BK. Is exercise effective for weight loss with ad libitum diet? Energy balance, compensation, and gender differences. *Exerc Sport Sci Rev* 2005; **33**: 169–174.
21. Ballor DL, Keesey RE. A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. *Int J Obes (Lond)* 1991; **15**: 717–726.
22. Simoneau JA, Lortie G, Boulay MR, Marcotte M, Thibault MC, Bouchard C. Inheritance of human skeletal muscle and anaerobic capacity adaptation to high-intensity intermittent training. *Int J Sports Med* 1986; **7**: 167–171.
23. Sisson SB, Katzmaryk PT, Earnest CP, Bouchard C, Blair SN, Church TS. Volume of exercise and fitness non-response in sedentary post-menopausal women. *Med Sci Sports Exerc* 2009; **41**: 539–545.
24. Atkinson G, Batterham A. True and false interindividual differences in the physiological response to an intervention. *Exp Physiol* 2015; **100**: 577–588.
25. Williamson PJ, Atkinson G, Batterham AM. Inter-individual responses of maximal oxygen uptake to exercise training: a critical review. *Sports Med* 2017; **47**: 1501–1513.
26. King NA, Horner K, Hills AP *et al.* Exercise, appetite and weight management: understanding the compensatory responses in eating behaviour and how the contribute to variability in exercise-induced weight loss. *Br J Sports Med* 2012; **46**: 315–322.
27. Hopkins W. Individual responses made easy. *J Appl Physiol* (1985) 2015; **118**: 1444–1446.
28. Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700.
29. Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
30. Ryan R. Cochrane Consumers and Communication Review Group. Cochrane Consumers and Communication Review Group reviews: how to consider equity issues. http://cccrg.cochrane.org, February 2013 (accessed 15th April 2017).
31. Higgins JPT. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol* 2008; **37**: 1158–1160.
32. IntHout J, Ioannidids JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analyses. *BMJ Open* 2016; **6**: e010247.
33. Jensen MD, Ryan DH, Apovian CM *et al.* AHA/ACC/TOS guideline for the management of overweight and obesity in adults. A report of the American Cardiology/American Heart Association task force on practice guidelines and the Obesity Society. *Circulation* 2014; **129**: S102–S138.
34. Hopkins WG, Marshall SW, Batterham AM, Hanin J. Progressive statistics for studies in sports medicine and exercise science. *Med Sci Sports Exerc* 2009; **41**: 3–12.
35. Schuit AJ, Schouten EG, Miles TP, Evans WJ, Saris WH, Kok FJ. The effect of six months training on weight, body fatness and serum lipids in apparently healthy elderly Dutch men and women. *Int J Obes (Lond)* 1998; **22**: 847–853.
36. Maiorana A, O'Driscoll G, Dembo L, Goodman C, Taylor R, Green D. Exercise training, vascular function, and functional

capacity in middle-aged subjects. *Med Sci Sports Exerc* 2001; **33**: 2022–2028.
37. Donnelly JE, Hill JO, Jacobsen DJ *et al.* Effects of a 16-month randomized controlled exercise trial on body weight and composition in young, overweight men and women: the Midwest Exercise Trial. *Arch Intern Med* 2003; **163**: 1343–1350.
38. Potteiger JA, Jacobsen DJ, Donnelly JE, Hill JO. Glucose and insulin responses following 16 months of exercise training in overweight adults: the Midwest Exercise Trial. *Metabolism* 2003; **52**: 1175–1181.
39. Schmitz KH, Jensen MD, Kugler KC, Jeffrey RW, Leon AS. Strength training for obesity prevention in midlife women. *Int J Obes (Lond)* 2003; **27**: 326–333.
40. Takeshima N, Rogers ME, Islam MM, Yarmauchi T, Watanabe E, Okada A. Effect of concurrent aerobic and resistance circuit exercise training on fitness in older adults. *Eur J Appl Physiol* 2004; **93**: 173–182.
41. Toraman NF, Erman A, Agyar E. Effects of multicomponent training on functional fitness in older adults. *J Aging Phys Act* 2004; **12**: 538–553.
42. Shojaee-Moradie F, Baynes KCR, Pentecost C *et al.* Exercise training reduces fatty acid availability and improves the insulin sensitivity of glucose metabolism. *Diabetologia* 2007; **50**: 404–413.
43. McTiernan A, Sorensen B, Irwin ML *et al.* Exercise effect on weight and body fat in men and women. *Obesity* 2007; **15**: 1496–1512.
44. Nalbant Ö, Toraman NF, Öğü C *et al.* Vitamin E and aerobic exercise: effects on physical performance in older adults. *Aging Clin Exp Res* 2009; **21**: 111–121.
45. Coker RH, Williams RH, Yeo SE *et al.* The impact of exercise training compared to caloric restriction on hepatic and peripheral insulin resistance in obesity. *J Clin Endocrinol Metab* 2009; **94**: 4258–4266.
46. Kerksick CM, Wismann-Bunn J, Fogt D *et al.* Changes in weight loss, body composition and cardiovascular disease risk after altering macronutrient distributions during a regular exercise program in obese women. *Nutr J* 2010; **9**: 59.
47. Atashak S, Peeri M, Jafari A, Ali Azarbayjani M. Effects of ginger supplementation and resistance training on lipid profiles and body composition in obese men. *J Med Plant Res* 2011; **5**: 3827–3832.
48. Sheikholeslami Vatani D, Ahmadi S, Ahmadi Dehrashid K, Gharibi F. Changes in cardiovascular risk factors and inflammatory markers of young, healthy, men after six weeks of moderate or high intensity resistance training. *J Sports Med Phys Fitness* 2011; **51**: 696–700.
49. Donges CE, Duffield R. Effects of resistance or aerobic exercise training on total and regional body composition in sedentary overweight middle-aged adults. *Appl Physiol Nutr Metab* 2012; **37**: 499–509.
50. Tracy BL, Hart CE. Bikram yoga training and physical fitness in healthy young adults. *J Strength Cond Res* 2013; **27**: 822–830.
51. Herring LY, Wagstaff C, Scott A. The efficacy of 12 weeks supervised exercise in obesity management. *Clin Obes* 2014; **4**: 220–227.
52. Kim YS, Nam JS, Yeo DW, Kim KR, Suh SH, Ahn CW. The effects of aerobic exercise training on serum osteocalcin, adipocytokines and insulin resistance on obese young males. *Clin Endocrinol (Oxf)* 2015; **82**: 686–694.
53. Bittari ST, Maeda SS, Marone MM, Santili C. Physical exercises with free weights and elastic bands can improve body composition parameters in postmenopausal women: WEB protocol with a randomized controlled trial. *Menopause* 2016; **23**: 383–389.
54. Tan S, Wang J, Cao L, Guo Z, Wang Y. Positive effect of exercise training at maximal fat oxidation intensity on body composition and lipid metabolism in overweight middle-aged women. *Clin Physiol Funct Imaging* 2016; **36**: 225–230.
55. Atlantis E, Chow CM, Kirby A, Fiatarone Singh MA. Worksite intervention effects on physical health: a randomised controlled trial. *Health Promot Int* 2006; **21**: 191–200.
56. Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, Blair SN. Changes in weight, waist circumference and compensatory responses with different doses of exercise amongst sedentary, overweight postmenopausal women. *PLoS One* 2009; **4**: e4515. https://doi.org/10.1371/journal.pone.0004515.
57. Tan S, Wang X, Wang J. Effects of supervised exercise training at the intensity of maximal fat oxidation in overweight young women. *J Exerc Sci Fit* 2012; **10**: 64–69.
58. Donnelly JE, Honas JJ, Smith BK *et al.* Aerobic exercise alone results in clinically significant weight loss for men and women: midwest exercise trial 2. *Obesity* 2013; **21**: E219–E228.
59. Prabhakaran B, Dowling EA, Branch JD, Swain DP, Leuthotz BC. Effect of 14 weeks of resistance training on lipid profile and body fat percentage in premenopausal women. *Br J Sports Med* 1999; **33**: 190–195.
60. Schmitz KH, Ahmed RL, Yee D. Effects of a 9-month strength training intervention on insulin, insulin-like growth factor (IGF)-I, IGF-binding protein (IGFPB)-I, and IGFBP-3 in 30–50-year old women. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 1597–1604.
61. Teixeira PJ, Going SB, Houtkooper LB *et al.* Resistance training in postmenopausal women with and without hormone therapy. *Med Sci Sports Exerc* 2003; **35**: 555–562.
62. Dognes CE, Duffield R, Drinkwater EJ. Effects of resistance training or aerobic training on interleukin-6, c-reactive protein, and body composition. *Med Sci Sports Exerc* 2010; **42**: 3014–3013.
63. Lockwood CM, Moon JR, Tobkin SE *et al.* Minimal nutrition intervention with high-protein/low-carbohydrate and low fat, nutrient-dense food supplement improves body composition and exercise benefits in overweight adults: a randomized controlled trial. *Nutr Metab* 2008; **5**. https://doi.org/10.1186/1743-7075-5-11.
64. Burtscher M, Gatterer H, Kunczicky H, Brandstatter E, Ulmer H. Supervised exercise in patients with impaired fasting glucose: impact on exercise capacity. *Clin J Sport Med* 2009; **19**: 394–398.
65. Vilela BL, Silva AABS, de Lira CAB, Andrade Mdos S. Workplace exercise and educational program for improving fitness outcomes related to health in workers: a randomized controlled trial. *J Occup Environ Med* 2015; **57**: 235–240.
66. Baillot A, Mampuya WM, Dionne IJ, Corneau E, Mexiat-Burdin A, Langlois MF. Impacts of supervised exercise training in addition to interdisciplinary lifestyle management in subjects awaiting bariatric surgery: a randomized controlled study. *Obes Surg* 2016; **26**: 2602–2610.
67. Dalager T, Justesen JB, Murray M, Boyle E, Siogaard GL. Implementing intelligent physical exercise training at the workplace: health effects among office workers—a randomized controlled trial. *Eur J Appl Physiol* 2016; **116**: 1433–1442.
68. Glowacki SP, Martin SE, Maurer A, Baek W, Green JS, Crouse SF. Effects of resistance, endurance, and concurrent exercise on training outcomes in men. *Med Sci Sports Exerc* 2004; **36**: 2119–2127.
69. Boutcher S. High-intensity intermittent exercise and fat loss. *J Obes* 2011; https://doi.org/10.1155/2011/868305.
70. Libardi CA, De Souza GV, Cavaglieri CR, Madruga VA, Chacon-Mikahil MP. Effect of resistance, endurance, and

concurrent training on TNF-a, IL-6, and CRP. *Med Sci Sports Exerc* 2012; **44**: 50–56.
71. Dolzeal BA, Potteiger JA. Concurrent resistance training and endurance training influence basal metabolic rate in nondieting individuals. *J Appl Physiol* (1985) 1998; **85**: 695–700.
72. Keating SE, Johnson NA, Mielke GI, Coombes JS. A systematic review and meta-analysis of interval training versus moderate-intensity continuous training on body adiposity. *Obes Rev* 2017; **18**: 943–964. https://doi.org/10.1111/obr.12536.
73. Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Soc Ser A Stat Soc* 2009; **172**: 137–159.
74. Partlett C, Riley RD. Random effects meta-analysis: coverage performance of 95% confidence and prediction intervals following REML estimation. *Stat Med* 2017; **36**: 301–317.
75. Fisher DJ, Carpenter R, Morris TP, Freeman SC, Tierney JF. Meta-analytical methods to identify who benefits most from treatments: daft, deluded or deft approach? *BMJ* 2017; **356**: j573.
76. Petkova E, Tarpey T, Huang L, Deng L. Interpreting meta-regression: application to recent controversies in antidepressants' efficacy. *Stat Med* 2013; **32**: 2875–2892.

References

Agurs-Collins T, Khoury MJ, Simon-Morton D, Olster DH, Harris JR, Milner JA (2008) Public health genomics: Translating obesity genomics research into population benefits. *Obesity* **16** (S3) S85-94.

Alberti KG, Zimmet P, Shaw J (2007) International diabetes federation: a consensus on type 2 diabetes prevention. *Diabetic Medicine* **24** 451-63.

Allen MT, Stoney CM, Owens JF Matthews KA (1993) Hemodynamic adjustments to laboratory stress: the influence of gender and personality. *Psychosomatic Medicine* **55** 505-17.

Alvarez C, Ramirez-Campillo R, Ramirez-Velez R, Izquierdo M (2017) Effects and prevalence of non-responders after 12 weeks of high-intensity interval or resistance training in adult women with insulin resistance: A randomized trial. *Journal of Applied Physiology* **122** 985-96.

American College of Sports Medicine (2012) ACSM's resource manual for guidelines for exercise testing and prescription. 7th edition. Philadelphia: Lippincott, Williams & Williams.

Anastos K, Charney P, Charon RA, Cohen E, Jones CY, Marte C, Swiderski DM, Wheat ME, Williams S (1991) Hypertension in women: what is really known? The women's caucus, working group on women's health of the society of general internal medicine. *Annals of Internal Medicine* **115** 287-93.

An Overview of The Human Gene Project. https://www.genome.gov/12011238/an-overview-of-the-human-genome-project/. Accessed 15th September 2017.

Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, Stevens VJ, Vollmer WM, Lin PH, Svetkey LP & Young DR (2003) Effects of comprehensive lifestyle modification on blood pressure control. Main results of the PREMIER clinical trial. *JAMA* **289** 2083-93.

Arnason V (2012) The personal is political: ethics and personalized medicine. *Ethical Perspectives* **19** 103-22.

Astorino TA, Schubert MM (2014) Individual responses to completion of short-term and chronic interval training: A retrospective study. *PLoS One* **9** e97638.

Atashak S, Peeri M, Jafari A, Ali Azarbayjani M (2011) Effects of ginger supplementation and resistance training on lipid profiles and body composition in obese men. *Journal of Medicinal Plants Research* **5** 3827-32.
Atkinson G, Batterham A (2015) True and false interindividual differences in the physiological response to an intervention. *Experimental Physiology* **100** 577-88.
Atkinson G. Loenneke JP, Fahs CA, Abe T, Rossow LM (2015) Individual differences in the exercise-mediated blood pressure response: Regression to the mean in disguise? *Clinical Physiology and Functional Imaging* **35** 490-2.
Atkinson G, Taylor C (2011) Normalization effect of sports training on blood pressure in hypertensive individuals: Regression to the mean? *Journal of Sports Sciences* **29** 643-4.
Atlantis E, Chow CM, Kirby A, Fiatarone Singh MA (2006) Worksite intervention effects on physical health: a randomised controlled trial. *Health Promotion International* **21** 191-200.
Baillot A, Mampuya WM, Dionne IJ, Corneau E, Mexiat-Burdin A, Langlois MF (2016) Impacts of supervised exercise training in addition to interdisciplinary lifestyle management in subjects awaiting bariatric surgery: a randomized controlled study. *Obesity Surg*ery **26** 2602-10.
Bakker EA, Snoek JA, Meindersma EP, Hopman MTE, Bellersen L, Verbeek ALM, Thijssen DHJ, Eijsvogels TMH (2018) Absence of fitness improvement is associated with outcomes in heart failure patients. *Medicine and Science in Sports and Exercise* **50** 196-203.
Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV (2010) Clinician's guide to cardiopulmonary exercise testing in adults. *Circulation* **122** 191-225.
Baldwin J, Snow RJ, Febbraio MA (2000) Effect of training status and relative exercise intensity on physiological responses in men. *Medicine and Science in Sports and Exercise* **32** 1648-54.
Ballor DL, Keesey RE (1991) A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. *International Journal of Obesity* **15** 717-26.
Bammam MM, Hill VJ, Adams GR, Haddad F, Wetzstein CJ, Gower BA, Ahmed A, Hunter GR (2003) Gender differences in resistance training-induced myofiber

hypertrophy among older adults. *Journal of Gerontology: Biological Sciences* **58** 108-16.
Barbeau P, Gutin B, Litaker M, Owens S, Riggs S, Okuyama T (1999) Correlates of individual differences in body-composition changes resulting from physical training in obese children. *American Journal of Clinical Nutrition* ***69*** 705-11.
Barker RJ, Schofield MR (2008) Classifying individuals as physiological responders using hierarchical modelling. *Journal of Applied Physiology* **105** 555–60.
Barsh GS, Farooqi IS, O'Rahilly S (2000) Genetics of body-weight regulation. *Nature* **404** 644-51.
Barwell ND, Malkova D, Leggate M, Gill JM (2009) Individual responsiveness to exercise-induced fat loss is associated with change in resting substrate utilization. *Metabolism* **58** 1320-8.
Batterham AM, Hopkins WG (2006) Making meaningful inferences about magnitudes. *International Journal of Physiology and Performance* **1** 50-7.
Baumert P, Lake MJ, Stewart CE, Drust B, Erskine RM (2016) Genetic variation and exercise-induced muscle damage: Implications for athletic performance, injury and ageing. *European Journal of Applied Physiology* **116** 1595-625.
Bell KJL, Irwig L, Craig JC, Macaskill P (2008) Use of randomized trials to decide when to monitor response for a new treatment. *BMJ* **336** 361-5.
Benetos A, Laurent S, Asmar RG, Lacolley P (1997a) Large artery stiffness in hypertension. *Journal of Hypertension* **15** S89 –97.
Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetieere P, Guize L (1997b) Pulse pressure: A predictor of long-term cardiovascular mortality in a French male population. *Hypertension* **30** 1410-5.
Bennette C, Vickers A (2012) Against quartiles: Catergorization of continuous variables in epidemiologic research, and its discounts. *BMC* **12** 21.
Binder EF, Yarasheski KE, Steger-May K, Sinacore DR, Brown M, Schechtman KB, Holloszy JO (2005) Effects of resistance training on body composition in frail older adults: results of a randomized, controlled trial. *Journal of Gerentology* **60** 1425-31.
Bittari ST, Maeda SS, Marone MM, Santili (2016) Physical exercises with free weights and elastic bands can improve body composition parameters in postmenopausal women: WEB protocol with a randomized controlled trial. *Menopause* **23** 383-9.

Blaus A, Madabushi R, Pacanowski M, Rose M, Schuck RN, Stockbridge N, Temple R, Unger EF (2015) Personalized cardiovascular medicine today. A food and drug administration/center for drug evaluation and research perspective. *Circulation* **132** 1425-32.

Blomqvist N, Svardsudd K (1978) A new method for investigating the relation between change and initial value in longitudinal blood pressure data. II. comparison with other methods. *Scandinavian Journal of Social Medicine* **6** 125-9.

Blumenthal JA, Babyak MA, Hinderliter A, Watkins LL, Craighead L, Lin PH, Caccia C, Johnson J, Waugh R, Sherwood A (2010) Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular markers in men and women with high blood pressure: the ENCORE Study. *Archives of Internal Medicine* **170** 126-35.

Blundell JE, Stubbs RJ, Hughes DA, Whybrow S, King NA (2003) Cross talk between physical activity and appetite control: does physical activity stimulate appetite? *Proceedings of the Nutrition Society* **62** 651-61.

Bonafiglia JT, Rotundo MP, Whitall JP, Scribbans TD, Graham RB, Gurd BJ (2016) Inter-individual variability in the adaptive responses to endurance and sprint interval training: A randomized crossover study. *PLoS One* **11** e0167790.

Bouchard C (1983) Human adaptability may have a genetic basis. In: Landry F, (ed). *Health and risk estimation, risk reduction and health promotion. Proceedings of the 18th annual meeting of the society of prospective medicine*. Canadian Public Health Association: Ottawa, pp.463-76.

Bouchard C (1995) Individual differences in the response to regular exercise. *International Journal of Obesity Related Metabolic Disord*ers **19** S4:S5-S8.

Bouchard C (2012a) Genomic predictors of trainability. *Experimental Physiology* **97** 347-52.

Bouchard C, An P, Rice T, Skinner JS, Wilmore JH, Gagnon J, Perusse L, Leon AS, Rao DC (1999) Familial aggregation of $\dot{V}O_2$max response to exercise training: results from the HERITAGE study. *Journal of Applied Physiology (1985)* **7** 1003-8.

Bouchard C, Antunbes-Correa LM, Ashley EA, Franklin N, Hwang PM, Mattsson CM, Negaro CE, Phillips SA, Sarzynski MA, Wang PY, Wheeler MT (2015) Personalised preventive medicine: genetics and the response to regular exercise in preventive interventions. Progress in Cardiovascular Diseases **57** 337-46.

Bouchard C, Blair CN, Church TS, Earnest CP, Hagberg JM, Hakkinen K, Jenkins TJ, Karavirta L, Kraus WE, Leon AS, Rao DC, Sarzynski MA, Skinner JS, Slentz CA, Rankinen T (2012b) Adverse response to regular exercise: is it a rare or common occurrence? *Plos One* **7**.

Bouchard C, Daw E, Rice T, Perusse L, Gagnon J, Province MA, Leon AS, Rao DC, Skinner JS, Wilmore JH (1998) Familial resemblance for $\dot{V}O_2$max in the sedentary state: the HERITAGE family study. *Medicine and Science in Sports and Exercise* **30** 252-8.

Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J (1995) The HERITAGE family study: aims, design and measurement protocol. *Medicine and Science in Sports and Exercise* **27** 721-9.

Bouchard C, Lesange R, Lortie G, Simoneau JA, Hamel P, Boulay MR, Perusse L, Theriault G, Leblanc C (1986) Aerobic performance in brothers, dizygotic and monozygotic twins. *Medicine and Science in Sports and Exercise* **18** 639-45.

Bouchard C, Rankinen T (2001) Individual differences in response to regular physical activity. *Medicine and Science in Sports and Exercise* **33** S6 S452-3.

Bouchard C, Rankinen T, Chagnon YC, Rice T, Perusse L, Gagnon J, Borecki I, An P, Leon AS, Skinner JS, Wilmore JH, Province M, Rao DC (2000) Genomic scan for maximal oxygen uptake and its response to training in the HERITAGE family study. *Journal of Applied Physiology* **88** 551-9.

Bouchard C, Sarzynski MA, Rice TK, Kraus WE, Church TS, Sung YJ, Rao DC, Rankinen T (2011) Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. *Journal of Applied Physiology* **110** 1160-70.

Bouchard C, Savard R, Després JP, Tremblay A, LeBlanc C (1985) Body composition in adopted and biological siblings. *Human Biology* **57** 61-75.

Bouchard C, Tremblay A, Despres JP, Nadeau A, Lupien PJ, Theriault G, Dussault J, Moorjani S, Pinault S, Fournier G (1990) The response to long-term overfeeding in identical twins. *New England Journal of Medicine* **322** 1477-82.

Bouchard C, Tremblay A, Despres JP, Theriault G, Nadeau A, Lupien PJ, Moorjani S, Prud'homme D, Fournier G (1994) The response to exercise with constant energy intake in identical twins. *Obesity Research* **2** 400-10.

Bouchard C, Wolfarth B, Rivera MA, Gagnin J, Simoneau JA (2000) *Genetic determinants of endurance performance*. In: Shephard RJ, Astrand PO, editors.

Endurance in sport: encyclopaedia of sports medicine. Oxford: Blackwell Scientific. pp.223-42.
Boutcher S (2011) High-intensity intermittent exercise and fat loss. *Journal of Obesity* **doi:10.1155/2011/868305**.
Boutcher SH, Dunn SL (2009) Factors that may impede the weight loss response to exercise-based interventions. *Obesity Reviews* **10** 671-80.
Boutcher SH, Nugent FW (1993) Cardiac responses to trained and untrained males to a repeated psychological stressor. *Behavioural Medicine* **19** 21-9.
Boutcher YN, Boutcher SH (2017) Exercise intensity and hypertension: What's new? *Journal of Human Hypertension* **31** 157-64.
Bruce D, Laurance I, McGuiness M, Ridley M, Goldswain P (2003) Nutritional supplements after hip fracture: poor compliance limits effectiveness. *Clinical Nutrition* **22** 497-500.
Bryk AS, Raudenbush SW (1998) Heterogeneity of variance in experimental studies: A challenge to conventional interpretations. *Psychological Bulletin* **104** 396-404.
Byrne NM, Meerkin JD, Laukkanen R, Ross R, Fogelholm M, Hills AP (2006) Weight loss strategies for obese adults: personalized weight management program vs. standard care. *Obesity* **14** 1777-88.
Buford TW, Roberts MD, Church TS (2013) Toward exercise as personalised medicine. *Sports Medicine* **43** 157-65.
Burl VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D (1995) Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey. *Hypertension* **25** 305-15.
Burtscher M, Gatterer H, Kunczicky H, Brandstatter E, Ulmer H (2009) Supervised exercise in patients with impaiured fasting glucose: impact on exercise capacity. *Clinical Journal of Sports Medicine* **19** 394-8.
Cardon LR, Carmelli D, Fabsitz RR, Reed T (1994) Genetic and environmental correlations between obesity and body fat distribution in adult male twins. *Human Biology* **66** 465-79.
Cardoso Jr CG, Gomides RS, Queiroz ACC, Pinto LG, da Silveira Lobo F, Tinucci T, Mion D Jr, de Moraes Forjaz CL (2010) Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinics* **65** 317-25.

Carpio-Rivera E, Moncada-Jiménez J, Salazar-Rojas W, Solera-Hererra A (2016) Acute Effects of Exercise on Blood Pressure: A Meta-Analytic Investigation. *Arquivos Brasileiros de Cardiologia* **106** 422–33.

Carroll D, Phillips AC, Der G (2008) Body mass index, abdominal adiposity, obesity, and cardiovascular reactions to psychological stress in a large community sample. Psychosomatic Medicine **70** 653-60.

Carroll D, Phillips AC, Der G, Hunt K, Benzeval M (2011). Blood pressure reaction to acute mental stress and blood pressure status: data from the 2-year follow-up of the West of Scotland study. *Psychosomatic Medicine* **73** 737-42.

Casperson CJ, Powell KE, Christenson GM (1985) Physical activity and physical fitness: Definitions and distinctions for health-related research. *Public Health Reports* **100** 126-31.

Caudwell P, Hopkins M, King NA, Stubbs RJ, Blundell JE (2009) Exercise alone is not enough: weight loss also needs a healthy (Mediterranean) diet? *Public Health Nutrition* **12** 1663-6.

Caudwell P, Gibbons C, Finlayson G, Naslund E, Blundell J (2014) Exercise and weight loss: No sex differences in body weight response to exercise. *Exercise and Sport Sciences Reviews* **42** 92-101.

Caudwell P, Gibbons C, Hopkins M, King N, Finlayson G, Blundell JE (2013) No sex difference in body fat in response to supervised and measured exercise. *Medicine and Science in Sports and Exercise* **45** 351-8.

Cauldfield T (2015) The obesity gene and the (misplaced) search for a personalized approach to our weight gain problems. *Wake Forest Journal* **5** 125-46.

Chan IS, Ginsburg GS (2011) Personalized medicine: progress and promise. *Annual Review of Genomics and Human Genetics* **12** 217-44.

Chen YL, Liu YF, Huang CY, Lee SD, Chan YS, Chen CC, Harris B, Kuo CH (2010) Normalization effect of sports training on blood pressure in hypertensives. *Journal of Sports Science* **28** 361-7.

Chiolero A, Paradis G, Rich B, Hanley JA (2013) Assessing the relationship between the baseline value of a continuous variable and subsequent change over time. Frontiers in Public Health **1** 1-8.

Church TS, Blair SN, Cocreham S, Johannsen N, Johnson W, Kramer K, Mikus CR, Myers V, Nauta M, Rodarte RQ, Sparks L, Thompson A, Earnest CP (2010) Effects

of aerobic and resistance training on haemoglobin A1c levels in patients with type 2 diabetes: a randomized control trial. *JAMA* **304** 2253-62.
Church TS, Earnest CP, Skinner JS, Blair SN (2007) Effects of different doses of activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized control trial. *JAMA* **297** 2081-91.
Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, Blair SN (2009) Changes in weight, waist circumference and compensatory responses with different doses of exercise amongst sedentary, overweight postmenopausal women. *PLos One* **4** e4515. **doi: 10.1371/journal.pone.0004515.**
Coker RH, Williams RH, Yeo SE, Kortebein PM, Bodenner DL, Kern PA, Evans WJ (2009) The impact of exercise training compared to caloric restriction on hepatic and peripheral insulin resistance in obesity. *Journal of Clinical Endocrinology and Metabolism* **94** 4258-66.
Collins FS, McKusick VA (2001) Implications of the Human Genome Project for medical science. *JAMA* **285** 540-4.
Collins FS, Varmus H (2015) A new initiative on precision medicine. New England Journal of Medicine **372** 793-5.
Craft LL, Perna FM (2004) The benefits of exercise for the clinically depressed. *Primary Care Companion Journal of Clinical Psychiatry* **6** 104-11.
Currie KD, Floras JS, La Gerche A, Goodman JM (2018) Exercise blood pressure guidelines: time to re-evaluate what is normal and exaggerated? *Sports Medicine* **doi:10.1007/s40279-018-0900-x.**
Dalager T, Justesen JB, Murray M, Boyle E, Siogaard GI (2016) Implementing intelligent physical exercise training at the workplace: health effects among office workers – a randomized controlled trial. *European Journal of Applied Physiology* **116** 1433-42.
Darne B, Girerd X, Safar M, Cambien F, Guize L (1989) Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. *Hypertension* **13** 392– 400.
Davidsen PK, Gallagher IJ, Hartman JW, Tarnopolsky MA, Dela F, Helge JW, Timmons JA, Phillips SM (2011) High responders to resistance training exercise training demonstrate differential regulation of skeletal muscle mRNA expression. *Journal of Applied Physiology* **110** 309-17.

Deighton K, King JA, Stensel DJ Jones B (2017) Expanding the investigation of meaningful effects in physiology research. *Future Science Open Access* **3** FS2018.
de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N (1999) Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* **99** 779–85.
Deram S, Vilares SM (2009) Genetic variants influencing effectiveness of weight loss strategies. *Arquivos Brasileiros de Endocrinologia & Metabologia* **53** 129-38.
Despres JP, Bouchard C, Savard R, Tremblay A, Marcotte M, Theriault G (1984) The effect of a 20-week endurance training program on adipose-tissue morphology and lipolysis in men and women. *Metabolism* **33** 235-9.
Despres JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodes-Cabau J, Bertrand OF, Poirier P (2008) Abdominal obesity and the metabolic syndrome: contribution to global cardio metabolic risk. *Arteriosclerosis, Thrombosis and Vascular Biology* **28** 1039-49.
Diamandis EP, Li M (2016) The side effects of translational omics: overtesting, overdiagnosis, overtreatment. *Clinical Chemistry and Laboratory Medicine* **54** 389-96.
Dokken BB, Tsao TS (2007) The physiology of body weight regulation: Are we too efficient for our own good? *Diabetes Spectrum* **20** 166-70.
Dolzeal BA, Potteiger JA (1998) Concurrent resistance training and endurance training influence basal metabolic rate in nondieting individuals. *Journal of Applied Physiology (1985)* **85** 695-700.
Donato K, Pi-Sunyer F, Becker D, NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (1998) Executive summary of the clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults. *Archives of Internal Medicine* **158** 1855-67.
Donges CE, Duffield R (2012) Effects of resistance or aerobic exercise training on total and regional body composition in sedentary overweight middle-aged adults. *Applied Physiology, Nutrition and Metabolism* **37** 499-509.
Donges CE, Duffield R, Drinkwater EJ (2010) Effects of resistance training or aerobic training on interleukin-6, c-reactive protein, and body composition. *Medicine and Science in Sports and Exercise* **42** 304-13.

Donnelly JE, Hill JO, Jacobsen DJ, Potteiger J, Sullivan DK, Johnson SL, Heelan K, Hise M, Fennessey PV, Sonko B, Sharp T, Jakicic JM, Blair SN, Tran ZV, Mayo M, Gibson C, Washburn RA (2003) Effects of a 16-month randomized controlled exercise trial on body weight and composition in young, overweight men and women: the Midwest Exercise Trial. *Archives of Internal Medicine* **163** 1343-50.

Donnelly JE, Honas JJ, Smith BK, Mayo MS, Gibson CA, Sullivan DK, Lee J, Herrmann SD, Lambourne K, Washburn RA (2013) Aerobic exercise alone results in clinically significant weight loss for men and women: Midwest Exercise Trial 2. *Obesity* **21** E219-28.

Donnelly JE, Smith BK (2005) Is exercise effective for weight loss with ad libitum diet? Energy balance, compensation, and gender differences. *Exercise and Sport Science Reviews* **33** 169-74.

Doucet E, Imbeault P, Alméras N, Tremblay A (1999) Physical Activity and low-fat diet: Is it enough to maintain weight stability in the reduced-obese individual following weight loss by drug therapy and energy restriction? *Obesity Research* **7** 323-33.

Douglas JA, Deighton K, Atkinson JM, Sar-Sarraf V, Stensel DJ, Atkinson G (2016) Acute exercise and appetite-regulating hormones in overweight and obese individuals: A meta-analysis. *Journal of Obesity* **2643625** **doi:10.1155/2016/2643625.**

Drapeau V, King N, Hetherington M, Doucet E, Blundell J, Tremblay A (2007) Appetite sensations and satiety quotient: predictors of energy intake and weight loss. *Appetite* **48** 159-66.

Dubach P, Froelicher VF, Klein J, Oakes D, Grover-McKay M, Friis R (1988) Exercise-induced hypertension in a male population. Criteria, causes and prognosis. *Circulation* **78** 1380-7.

Egbewale BE (2015) Statistical issues in randomised controlled trials: a narrative synthesis. *Asian Pacific Journal of Tropical Biomedicine* **5** 354-9.

Ells LJ, Demaio A, Farpour-Lambert N (2018) Diet, genes, and obesity. *BMJ* **260** **k7. doi:10.1136/bmj.k7.**

Erskine RM, Jones DA, Williams AG, Stewart CE, Degens H (2010) Inter-individual variability in the adaptation of human muscle specific tension to progressive resistance training. *European Journal of Applied Physiology* **110** 1117-25.

Fagard RH. Physical activity, physical fitness and the incidence of hypertension (2005). *Journal of Hypertension* **23** 265-7.
Feero WG (2017) Introducing "genomics and precision health'. *JAMA* **317** 1842-3.
Feitosa MF, Gaskill SE, Rice T, Rankinen T, Bouchard C, Rao DC, Wilmore JH, Skinner JS, Leon AS (2002) Major gene effects on exercise ventilatory threshold: the HERITAGE family study. *Journal of Applied Physiology (1985)* **93** 1000-6.
Finlayson G, Bryant E, Blundell JE, King NA (2009) Acute compensatory eating following exercise is associated with implicit hedonic wanting for food. *Physiology and Behaviour* **97** 62-7.
Fisher DJ, Carpenter R, Morris TP, Freeman SC, Tierney JF (2017) Meta-analytical methods to identify who benefits most from treatments: daft, deluded or deft approach? *BMJ* **356** j573.
Fiuza-Luces C, Garatachea N, Berger NA, Lucia A (2013) Exercise is the real polypill. *Physiology* **28** 330-58.
Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, Coke LA, Fleg JL, Forman DE, Gerber TC, Gulati M, Madan K, Rhodes J, Thompson PD, Williams MA (2012) Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation* **128** 873-934.
Flores M, Glusman G, Brogaard K, Price ND, Hood L (2013) P4 medicine: how systems medicine will transform the healthcare sector and society. Personalized Medicine **10** 565-76.
Franklin SS, Gustin W IV, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D (1997) Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation* **96** 308-15.
Franklin SS, Khan SA, Wong ND, Larson MG, Levy D (1999) Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* **100** 354 –60.
Frese EM, Fick A, Sadowsky HS (2011) Blood pressure measurement guidelines for physical therapists. *Cardiopulmonary Physical Therapy Journal* **22** 5-12.
Gagnon J, Province MA, Bouchard C, Leon AS, Skinner JS, Wilmore JH, Rao DC (1996) The HERITAGE family study: quality assurance and quality control. *Annals of Epidemiology* **6** 520-9.

Gaskill SE, Rice T, Bouchard C, Gagnon J, Rao DC, Skinner JS, Wilmore JH, Leon AS (2001) Familial resemblance in ventilatory threshold: the HERITAGE family study. *Medicine and Science in Sports and Exercise* **233** 1832-40.
Gayagay G, Yu B, Hambly B, Boston T, Hahn A, Celermajer DS, Trent RJ (1998) Elite endurance athletes and the ACE I allele-the role of genes in athletic performance. *Human* Genetics **103** 48-50.
Ghosh S, Vivar JC, Sarzynski MA, Sung YJ, Timmons JA, Bouchard C, Rankinen T (2013) Integrative pathway analysis of a genome-wide association study of $\dot{V}O_2$max response to exercise training. Journal of Applied Physiology (1985) **115** 1343-59.
Glowacki SP, Martin SE, Maurer A, Baek W, Green JS, Crouse SF (2004) Effects of resistance, endurance, and concurrent exercise on training outcomes in men. *Medicine and Science in Sports and Exercise* **36** 2119-27.
Gobel FL, Nordstrom LA, Nelson RR, Jorgensen CR, Wang Y (1978) The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* **57** 549-56.
Goltz FR, Thackray AE, King JA, Dorling JL, Atkinson G, Stensel DJ (2018) Interindividual responses of appetite to acute exercise: a replicated crossover study. *Medicine and Science in Sports and Exercise* **50** 758-68.
Goran MI, Poehlman ET (1992) Endurance training does not enhance total energy expenditure in healthy elderly persons. *American Journal of Physiology-Endocrinology and Metabolism* **263** E950-7.
Gurd BJ, Giles MD, Bonafiglia JT, Raleigh JP, Boyd JC, Ma JK, Zelt JG, Scibbans TD (2016) Incidence of nonresponse and individual patterns of response following sprint interval training. *Journal of Applied Nutrition and Metabolism* **41** 229-34.
Guyatt GH, Heyting A, Jaeschke R, Keller J, Adachi JD, Roberts RS (1990) N–of-1 randomized trials for investigating new drugs. *Controlled Clinical Trials* **11** 88-100.
Hagberg JM, Ferrell RE, Dengel DR, Wilund KR (1999) Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. *Hypertension* **34** 18-23.
Hagobian TA, Braun B. Physical activity and hormonal regulation of appetite: Sex differences and weight control. *Exercise and Sport Sciences Reviews* **38** 25-30.
Hagobian TA, Sharoff CG, Stephens BR, Wade GN, Silva JE, Chipkin SR, Braun B (2009) Effects of exercise on energy-regulating hormones and appetite in men and

women. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology* **296** R233-42.
Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL, Swinburn BA (2011) Quantification of the effect of energy imbalance on bodyweight. *The Lancet* **378** 826-37.
Hamburg MA, Collins GS (2010) The path to personalized medicine. *New England Journal of Medicine* **353** 301-4.
Hamel P, Simoneau J, Lortie G, Boulay MR, Bouchard C (1986) Heredity and muscle adaptation to endurance training. *Medicine and Science in Sports and Exercise* **18** 690-6.
Hamer M, Taylor A, Steptoe A (2006) The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. *Biological Psychology* **71** 183-90.
Harrell F (2018) Viewpoints on heterogeneity of treatment effect and precision medicine. http://www.fharrell.com/post/hteview/#fn:Under-the-best-o. Accessed 7th June 2018.
Hautala AJ, Makikallio TH, Kiviniemi A, Laukkanen RT, Nissila S, Huikuir HV, Tulppo MP (2003) Cardiovascular autonomic function correlates with the response to aerobic training in healthy subjects. *American Journal of Physiology. Heart and Circulatory Physiology* **285** 1747-52.
Hautala AJ, Kiviniemi AM, Makikallio TH, Kinnunen H, Nissila S, Huikuri HV, Tulppo MP (2006) Individual differences in the responses to endurance and resistance training. *European Journal of Applied Physiology* **96** 535-42.
Hecksteden A, Krauscher J, Scharhag - Rosenberger F, Theisen D, Senn S, Meyer T (2015) Individual response to exercise training – a statistical perspective. *Journal of Applied Physiology (1985)* **118** 1450-9.
Hecksteden A, Pitsch W, Rosenberger F, Meyer T (2018) Repeated testing for the assessment of individual response to exercise training. *Journal of Applied Physiology* **124** 1567-79.
Heini AF, Kirk KA, Lara-Castro C, Weinsier RL (1998) Relationship between hunger-satiety feelings and various metabolic parameters in women with obesity during controlled weight loss. *Obesity Research* **6** 225-30.

Heller DA, De Faire U, Pederson NL, Dahlen G, McLearn GE (1993) Genetic and environmental influences on serum lipid levels in twins. *New England Journal of Medicine* **328** 1150-6.
Henry JB, Miller MC, Kelly KC, Champney D (2002) Mean arterial pressure (MAP): an alternative and preferable measurement to systolic blood pressure (SBP) in patients for hypotension detection during hemapheresis. *Journal of Clinical Apheresis* **17** 55-64.
Herring LY, Wagstaff C, Scott A (2014) The efficacy of 12 weeks supervised exercise in obesity management. *Clinical Obesity* **4** 220-7.
Higgins JPT (2008) Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *International Journal of Epidemiology* **37** 1158-60.
Higgins JPT, Green S (eds) (2011) *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from http://handbook.cochrane.org.
Higgins JPT, Thompson SG, Spiegelhalter DJ (2009) A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society. Series A (Statistics in Society)* **172** 137–59.
Hill JO, Melanson EL (1999) Overview of the determinants of overweight and obesity: Current evidence and research issues. *Medicine and Science in Sports and Exercise* **311** S515-21.
Hinney A, Vogel CI, Hebebrand J (2010) From monogenic to polygenic obesity: recent advances. *European Child and Adolescent Psychiatry* **19** 297-310.
Hoffman J, Rataess N, Kang J, Mangine G, Faigenbaum A, Stout J (2006) Effects of creatine and B-alanine supplementation on performance and endocrine responses in strength/power athletes. *International Journal of Sport Nutrition and Exercise Metabolism* **16** 430-46.
Hong Y, Pederson NL, Brismar K, de Faire U (1997) Genetic and environmental architecture of the features of the insulin-resistance syndrome. *American Journal of Human Genetics* **60** 143-52.
Hood L, Lovejoy JC, Price ND (2015) Integrating big data and actionable health coaching to optimize wellness. *BMC Medical* **13** 4.
Hopkins M, Blundell J, Halford J, King N, Finlayson G (2016) The regulation of food intake in humans. In: De Groot LJ, Chrousos G, Dungan K, et al., editors.

Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278931/
Hopkins M, Blundell J, King NA (2014) Individual variability in compensatory eating following acute exercise in overweight and obese women. *British Journal of Sports Medicine* **48** 1472-6.
Hopkins W (2000) Precision of the estimate of a subject's true value (Excel spreadsheet). In: *A new view of statistics.*
Hopkins W (2004) How to interpret changes in an athletic performance test. *Sportsci.org* **8** 1-7.
Hopkins W (2015) Individual responses made easy. *Journal of Applied Physiology (1985)* **118** 1444-6.
Hopkins W, Batterham AM (2018) The vindication of magnitude-based inference. **22** *Sportsci.org* 19-29.
Hopkins WG, Marshall SW, Batterham AM, Hanin J (2009) Progressive statistics for studies in sports medicine and exercise science. *Medicine and Science in Sports and Exercise* **41** 3-12.
Huang CJ, Webb HE, Zourdos MC, Acevedo EO (2013) Cardiovascular reactivity, stress and physical activity. *Frontiers in Physiology* **4**:314.
Huang Z, Willett WC, Manson JE, Rosner B, Stampfer MJ, Speizer FE, Colditz GA (1998) Body weight, weight change, and risk for hypertension in women. *Annals of Internal Medicine* **128** 81-8.
Hubal MJ, Gordish-Dressman H, Thompson PD, Price TB, Hoffman EP, Angelopoulous TJ, Gordon PM, Moyna NM, Pescatello LS, Visch PS, Zoeller RF, Seip RL, Clarkson PM (2005) Variability in muscle size and strength gain after unilateral resistance training. *Medicine and Science in Sports and Exercise* **37** 964-72.
Imboden MT, Harber MP, Whaley MH, Finch WH, Bishop DL, Kaminslky LA (2018) Cardiorespiratory fitness and mortality in healthy men and women. *Journal of the American College of Cardiology* **72** 2283-92.
IntHout J, Ioannidis JP, Rovers MM, Goeman JJ (2016) Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* **6** e010247.
Jae SY, Fernhall B, Heffernan KS, Kang M, Lee MK, Choi YH, Hong KP, Ahn ES, Park WH (2006) Exaggerated blood pressure response to exercise is associated with carotid atherosclerosis in apparently healthy men. *Journal of Hypertension* **24** 881-7.

Jae SY, Franklin BA, Choo J, Choi YH, Fernhall B (2015) Exaggerated exercise blood pressure response during treadmill testing as a predictor of future hypertension in men: a longitudinal study. *American Journal of Hypertension* **28** 1362-7.
Jameson JL, Longo DL (2015) Precision medicine – personalized, problematic, and promising. *New England Journal of Medicine* **70** 612-4.
Janssens ACJW, Gwinn M, Bradley LA, Oostra BA, van Dujin CM, Khoury MJ (2008) A critical appraisal of the scientific basis of commercial genomic profiles. *American Journal of Human Genetics* **82** 593-9.
Jaquet F, Goldstein IB, Shapiro D (1998) Effects of age and gender on ambulatory blood pressure and heart rate. *Journal of Human Hypertension* **12** 253-7.
Jensen MD, Ryan DH, Apovian CM, Ard JD, Commuzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, Jordan HS, Kendall KA, Lux LJ, Mentor-Marcel R, Morgan LC, Trisolini MG, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Selke FW, Shen WK, Smith SC Jr, Tomaselli GF (2014) 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. A report of the American Cardiology/American Heart Association task force on practice guidelines and the Obesity Society. *Circulation* **129** S2 S102-38.
Jette M, Sidney K, Blumchen G (1990) Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clinical Cardiology* **13** 555-65.
Jequier E, Teppy L (1999) Regulation of body weight in humans. *Physiology Reviews* **79** 451-80.
Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (1997) The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Archives of Internal Medicine* **157** 2413–46.
Jones H, Atkinson G, Leary A, George K, Murphy M, Waterhouse J (2006) Reactivity of ambulatory blood pressure to physical activity varies with time of day. *Hypertension* **47**:778-84.

Jones H, George K, Edwards B, Atkinson G (2007) Is the magnitude of acute post-exercise hypotension mediated by exercise intensity or total work done? *European Journal of Applied Physiology* **102** 33-40.
Jones H, Pritchard C, George K, Edwards B, Atkinson G (2008) The acute post-exercise response of blood pressure varies with time of day. *European Journal of Applied Physiology* **104** 481-9.
Jones H, Taylor CE, Lewis NC, George K, Atkinson G (2009) Post-exercise blood pressure reduction is greater following intermittent than continuous exercise and is influenced less by diurnal variation. *Chronobiology International* **26** 293-306.
Joyner MJ (2016) Precision medicine, cardiovascular disease and hunting elephants. *Progress in Cardiovascular Disease* **6** 651-60.
Joyner MJ, Paneth N (2015) Seven questions for personalized medicine. *JAMA* **314** 999-1000.
Kainulainen H (2009) Run more, perform better – old truth revisited. *Journal of Applied Physiology (1985)* **106** 1477-8.
Karanja NM, Obarzanek E, Lin PH, McCullough ML, Phillips KM, Swain JF, Champagne CM, Hoben MP (1999) Descriptive characteristics of the dietary patterns used in the Dietary Approaches to Stop Hypertension trial. *Journal of the American Dietetic Association* **99** S19-27.
Karavirta L, Hakkinen K, Kauhanen A, Arija-Blazquez A, Sillanpaa E, Rinkinen N, Hakkinen A (2011) Individual responses to combined endurance and strength training in older adults. *Medicine and Science in Sports and Exercise* **43** 484-90.
Katsanis SH, Javitt G, Hudson K (2008) A case study of personalized medicine. *Science* **320**: 53-54.
Kaufman MP, Forster HV (1996) In: *Handbook of Physiology. Exercise: Regulation and Integration of Multiple Systems*. Eds Rowell Shepherd.
Keating SE, Johnson NA, Mielke GI, Coombes JS (2017) A systematic review and meta-analysis of interval training versus moderate-intensity continuous training on body adiposity. *Obeitys Reviews* **18** 943-64.
Kelley GA, Kelley KS (2008) Efficacy of aerobic exercise on coronary heart disease risk factors. *Preventative Cardiology* **11** 71-5.
Keogh B (2012) Era of personalized medicine may herald end of soaring cancer costs. Journal of the National Cancer Institute **104** 12-17.

Kerksick CM, Wismann-Bunn J, Fogt D, Thomas AR, Taylor L, Campbell BI, Wolborn CD, Harvey T, Toberts MD, La Bounty P, Galbreath M, Marcello B, Rasmussen CJ, Kreider RB (2010) Changes in weight loss, body composition and cardiovascular disease risk after altering macronutrient distributions during a regular exercise program in obese women. *Nutrition Journal* **9** 59.

Khoury MJ, Galea S (2016) Will precision medicine improve population health? *JAMA* **316** 1357-8.

Kim YS, Nam JS, Yeo DW, Kim KR, Suh SH, Ahn CW (2015) The effects of aerobic exercise training on serum osteocalcin, adipocytokines and insulin resistance on obese young males. *Clinical Endocrinology* **82** 686-94.

King N, Byrne NM, Hunt A, Hills A (2010) Comparing exercise prescribed with exercise completed: Effects of gender and mode of exercise. *Journal of Sports Sciences* **28** 633-40.

King NA, Caudwell P, Hopkins M, Byrne NM, Colley R, Hills AP, Stubbs JR, Blundell JE (2007a) Metabolic and behavioural compensatory responses to exercise interventions: barriers to weight loss. *Obesity* **15** 1373-83.

King NA, Hester J, Gately PJ (2007b) The effect of a medium-term activity-and diet-induced energy deficit on subjective appetite sensations in obese children. *International Journal of Obesity* **31** 334-9.

King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE (2008) Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss. *International Journal of Obesity* **32** 177-84.

King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE (2009) Beneficial effects of exercise: shifting the focus from body weight to other markers of health. *British Journal of Sports Medicine* **43** 924-7.

King NA, Horner K, Hills AP, Byrne NM, Wood RE, Bryant E, Caudwell P, Finlayson G, Gibbons C, Hopkins M, Martins C, Blundell JE (2012) Exercise, appetite and weight management: understanding the compensatory responses in eating behaviour and how the contribute to variability in exercise-induced weight loss. *British Journal of Sports Medicine* **46** 315-22.

Kittles R (2012) Genes and environments: moving towards personalized medicine in the context of health disparities. *Ethnicity and Disease* **22** (3S1):S1 43-6.

Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H (2009) Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *JAMA* **301** 2024-35.
Kohrt WM, Malley MT, Coggan AR, Spina RJ, Ogawa T, Ehsani AA, Bourey RE, Martin WH, Holloszy JO (1991) Effects of gender, age, and fitness level on response of $\dot{V}O_2$max to training in 60-71 yr-olds. *Journal of Applied Physiology (1985)* **71** 2004-11.
Kovolou GD, Kovolou V, Papadopoulou A, Watts GF (2016) MTP gene variants and response to lomitapide in patients with homozygous familial hypercholesterolemia. *Journal of Atherosclerosis and Thrombosis* **23** 878-83.
Lambiase MJ, Dorn J, Roemmich JN (2013) Systolic blood pressure reactivity during submaximal exercise and acute psychological stress in youth. *American Journal of Hypertension* **26** 409-15.
Laukkanen JA, Kurl S, Salonen R, Rauramaa R, Salonen JT (2004) The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective, population-based cohort study. *European Heart Journal* **5** 1428-37.
Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae YJ, Rauramaa R (2016) Long-term change in cardiorespiratory fitness and all-cause mortality: a population-based study. *Mayo Clinic Proceedings* **91** 1183-8.
Le VV, Mitiku T, Sungar G, Myers J, Froelicher V (2008) The blood pressure response to dynamic exercise testing. *Progress in Cardiovascular Diseases* **51** 135-60.
Leifer ES, Church TS, Earnest CP, Fleg JL, Hakkinen K, Karavirta L, Kraus WE, Mikus CR, Resnick B (2015) Adverse cardiovascular response to aerobic exercise training: is this a concern? *Medicine and Science in Sports and Exercise* **48** 20-5.
Lesage RJA, Simoneau J, Jobin J, Leblanc J, Bouchard C (1985) Familial resemblance in maximal heart rate, blood lactate and aerobic power. *Human Heredity* **35** 182-9.
Libardi CA, De Souza GV, Cavaglieri CR, Madruga VA, Chacon-Mikahil MP (2012) Effect of resistance, endurance, and concurrent training on TNF-a, IL-6, and CRP. *Medicine and Science in Sport and Exercise* **44** 50-6.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* **339**: b2700.

Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ (2011) The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? *Personalized Medicine* **8** 161-73.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Al Mozroa MA, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A (2012) A Comparative Risk Assessment of Burden of Disease and Injury Attributable to 67 Risk Factors and Risk Factor Clusters in 21 Regions, 1990-2010: A Systematic Analysis for the Global Burden of Disease Study 2010. *Lancet* **380** 2224-60.

Lima AH, Miranda AS, Correia MA, Soares AH, Cucato GG, Sobral Filho DC, Gomes SL, Ritti-Dias RM (2015) Individual blood pressure responses to walking and resistance exercise in peripheral artery disease patients: Are the mean values describing what is happening? *Journal of Vascular Nurs* **33** 150-6.

Lloyd Jones DM, Levy D (2007) In: *Epidemiology of Hypertension. Hypertension – A Companion to Braunwald's Heart Disease.* Eds Black Elliott.

Loenneke JP, Fahs CA, Abe T, Roscow LM, Ozaki H, Pujol TJ, Bemben MG (2014) Hypertension risk: exercise is medicine* for most but not all. *Clinical Physiology and Functional Imaging* **34** 77-81.

Lockwood CM, Moon JR, Tobkin SE, Walter AA, Smith AE, Dalbo VJ, Cramer JT, Stout JR (2008) Minimal nutrition intervention with high-protein/low-carbohydrate and low fat, nutrient-dense food supplement improves body composition and exercise benefits in overweight adults: a randomized controlled trial. *Nutrition and Metabolism* **5 doi: 10.1186/1743-7075-5-11.**

Loos RJ (2012) Genetic determinants of common obesity and their value in prediction. *Best Practice and Research Clinical Endocrinology and Metabolism **26*** 211-26.

Lortie G, Simoneau JA, Hamel P, Boulay MR, Landry F, Bouchard C (1984) Responses of maximal aerobic power and capacity to aerobic training. *International Journal of Sports Medicine* **5** 232-6.

Lucia A, Gomez-Gallego F, Barroso I, Rabadan M, Bandres F, San Juan AF, Chicharro JL, Ekelund U, Brage S, Earnest CP, Wareham NJ, Franks PW (2005) PPARGC1A genotype (Gly482Ser) predicts exceptional endurance capacity in European men. *Journal of Applied Physiology* **99** 344-8.
Macdiarmid JI, Cade JE, Blundell JE (1996). High and low-fat consumers, their macronutrient intake and body mass index: further analysis of the National Diet and Nutrition Survey of British Adults. *European Journal of Clinical Nutrition* **50** 505-12.
MacDonald JR (2002) Potential causes, mechanisms, and implications of post exercise hypotension. *Journal of Human Hypertension* **16** 225-36.
Maes HHM, Neale MC, Eaves LJ (1997) Genetic and environmental factors in relative body weight and human adiposity. *Behaviour Genetics* **27** 325-51.
Maiorana A, O'Driscoll G. Dembo L, Goodman C, Taylor R, Green D (2001) Exercise training, vascular function, and functional capacity in middle-aged subjects. *Medicine and Science in Sports and Exercise* **33** 2022-8.
Mann TN, Lamberts RP, Lambert MI (2014) High responders and low responders: factors associated with individual variation in response to standardized training. *Sports Medicine* **44** 1113-24.
Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasterneck A, Pikkarainen J, Romo M, Sjoblom T, Nikkila EA (1988) Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* **260** 641-51.
Manrai AK, Patel CJ, Ioannidis JP (2018) In the era of precision medicine and big data, who is normal? *JAMA* **319** 1981-2.
Marcon AR, Bieber M, Caulfield T (2018) Representing a “revolution”: how the popular press has portrayed personalized medicine. *Genetics in Medicine* **doi:10.1038/gim.2017.217**
Marti A, Moreno-Aliaga MJ, Hebebrand J, et al (2004) Genes, lifestyles and obesity. *International Journal of Obesity* **28** S29-S36.
Martinez JA (2000) Body weight regulation: Causes of obesity. *Proceedings of the Nutrition Society* **59** 337-45.
Martinez JA, Frühbeck G (1996) Regulation of energy balance and adiposity: a model with new approaches. *Revista Espanola de Fisiologia* **52** 255-58.

Matthew CE, Pate RR, Jackson KL, Ward DS, Macera CA, Kohl HW, Blair SN (1998) Exaggerated blood pressure response to dynamic exercise and risk of future hypertension. *Journal of Clinical Epidemiology* **51** 29-35.
Mauri L, Kereikakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SLT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krukoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM (2014) Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *New England Journal of Medicine* **371** 2155-66.
McCartney M (2017) Are we too captivated by precision medicine? *BMJ* **356** j1168. **doi: 10.1136/bmj.j1168.**
McGuire HL, SvetkeyLP, Harsha DW, Elmer PJ, Appel LJ, Ard JD (2004) Comprehensive lifestyle modification and blood pressure control: A review of the PREMIER trial. *Journal of Clinical Hypertens*ion **6** 383-90.
McGlory C, Phillips SM (2015) Exercise and the regulation of skeletal muscle hypertrophy. *Progress in Molecular Biology and Translational Science* **135** 153-73.
McTiernan A, Sorensen B, Irwin ML, Morgan A, Yasui Y, Rudoplh RE, Surawicz C, Lampe PD, Ayub K, Potter JD (2007) Exercise effect on weight and body fat in men and women. *Obesity* **15**: 1496-512.
Melanson EL, Keadle SK, Donnelly JE, Braun B, King NA (2013) Resistance to exercise-induced weight loss: compensatory behavioural adaptations. *Medicine and Science in Sports and Exercise* **45** 1600-9.
Mitchell CJ, Churchward-Venne TA, Bellamy L, Parise G, Baker SK, Phillips SM (2013) Muscular and systemic correlates of resistance training-induced muscle hypertrophy. 2013. *PLos One* **8;e78636.**
Miyamoto-Mikami E, Zempo H, Fuku N Kikuchi M, Murakami H (2018) Heritability estimates of endurance related phenotypes: A systematic review and meta-analysis. *Scandinavian Journal of Medicine in Science and Sports* **28** 834-45.
Mokdad AH, Ford ES, Bowman BA (2003) Prevalence of obesity, diabetes and obesity-related health risk factors, 2001. *JAMA* **289** 76-9.
Montalvo AM, Tse-Dinh YC, Liu Y, Swartzon M, Hechtman KS, Myer G (2017) Precision sports medicine: The future of advancing health and performance in youth and beyond. *Strength and Conditioning Journal* **39** 48-58.

Montero D, Ludby C (2017) Refuting the myth of non-response to exercise training: 'non-responders' do respond to higher dose of training. *Journal of Physiology* **595** 3377-87.

Montoye HJ, Gayle R (1978) Familial relationships in maximal oxygen uptake. *Human Biology* **50** 241-9.

Mori M, Higuchi K, Sakurai A, Tabara Y, Miki T, Nose H (2009) Genetic basis of inter-individual variability in the effects of exercise on the alleviation of lifestyle-related diseases. *Journal of Physiology* **587** 5577-84.

Myers CA, Johnson WD, Earnest CP, Rood JC, Tudoir-Locke C, Johannsen NM, Harris M, Church TS, Martin CK (2014) Examination of mechanisms (E-MECHANIC) of exercise-induced weight compensation: study protocol for a randomized control trial. *Trials* **15** 212.

Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE (2002) Exercise capacity and mortality among men referred for exercise testing. *New England Journal of Medicine* **346** 793-801.

Nalbant Ö, Toktas N, Toraman NF, Öğüs C, Aydin H, Kacar C, Ozkaya YG (2009) Vitamin E and aerobic exercise: effects on physical performance in older adults. *Aging Clinical and Experimental Research* **21** 111-21.

National Health England. Precision medicine: What is it and how will it be achieved? (2015) www.genomicseducation.hee.nhs.uk/news/item/138-precision-medicine-what-is-it-and-how-will-it-be-achieved. Accessed 29th September 2017.

National Institute of Health. All of Us Research Program (2015) https://www.nih.gov/research-training/allofus-research-program. Accessed 20th September 2017.

National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Washington (DC): National Academies Press (US); 2011. Appendix E, Glossary.

Norbury A, Seymour B (2018) Response heterogeneity: Challenges for personalized medicine and big data approaches in psychiatry and chronic pain. *F1000 Research* **7** 55.

Obarzanek E, Stacks FM, Vollmer WM, Bray GA, Miller EM, Lin PH, Karanja NM, Most-Windhauser MM, Moore TJ, Swain JF, Bales CW, Proschan MA (2001)

Effects on blood lipids of a blood-pressure lowering diet: The Dietary Approaches to Stop Hypertension (DASH) trial. *American Journal of Clinical Nutrition* **74** 80-9.
O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P (2005) Practical guidelines for the European Society of hypertension for clinic, ambulatory and self-blood pressure measurement. *Journal of Hypertension* **23** 697-701.
O'Neal WT, Qureshi WT, Blaha MJ, Keteyian SJ, Brawner CA, Al-Mallah MH (2015) Systolic blood pressure response during exercise stress testing: The Henry Ford Exercise Testing (FIT) Project. *JAHA* **7** pii: e002050. **doi: 10.1161/JAHA.115.002050.**
O'Rourke MF (1982) *Arterial Function in Health and Disease*. Edinburgh, UK: Churchill-Livingstone.
Palatini P (1988) Blood pressure behavior during physical activity. *Sports Medicine* **5** 353-74.
Pandey A, Ayers C, Blair SN, Swift DL, Earnest CP, Kitzman DW, Khera A, Church TS, Berry JD (2015) Cardiac determinants of heterogeneity in fitness change in response to moderate intensity aerobic exercise training. *Journal of the American College of Cardiology* **65** 1057-8.
Partlett C, Riley RD (2017) Random effects meta-analysis: Coverage performance of 95% confidence and prediction intervals following REML estimation. *Statistics in Medicine* **36** 301-17.
Pencina MJ, Peterson ED (2016) Moving from clinical trials to precision medicine. The role of predictive modelling. *JAMA* **315** 1713-4.
Perusse L, Gagnon J, Province MA, Rao DC, Wilmore HG, Leon AS, Bouchard C, Skinner JS (2001) Familial aggregation of submaximal aerobic performance in the HERITAGE family study. *Medicine and Science in Sports and Exercise* **33** 597-604.
Pescatello LS, Guidry MA, Blanchard BE, Kerr A, Taylor AL, Johnson AN, Maresh CM, Rodriquez N, Thompson PD (2004a) Exercise intensity alters postexercise hypotension. *Journal of Hypertension* **22** 1881-8.
Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA (2004b) Exercise and hypertension. *Medicine & Science in Sports & Exercise* **36** 533-53.

Pescatello LS (2014) American College of Sports Medicine. *Guidelines for Exercise Testing and Prescription.* 9th edn. Philadelphia, PA: Wouters Kluwer/Lippincott Williamson & Wilkins Health.

Peterson JA (2007) Get moving! Physical activity counseling in primary care. *Journal of the American Academy of Nurse Practitioners* **19** 349-57.

Petkova E, Tarpey T, Huang L, Deng L (2013) Interpreting meta-regression: application to recent controversies in antidepressants' efficacy. *Statistics in Medicine* **32** 2875-92.

Phillips BE, Kelly BM, Lilja M, Ponce-Gonzalez JG, Brogan RJ, Morris DL, Gustafsson T, Kraus WE, Atherton PJ, Vollaard NBJ, Rooyackers O, Timmons JA (2017) A practical and time-efficient high-intensity interval training program modifies cardio-metabolic risk factors in adults with risk factors for type II diabetes. *Frontiers in Endocrinology* **8 doi:10.83389/fendo.2017.00229.**

Phillips BE, Williams JP, Gustafsson T, Bouchard C, Rankinen T, Knudsen S, Smith K, Timmons JA, Atherton PJ (2013) Molecular networks of human muscle adaptation to exercise and age. *PLos Genetics* **e1003389.**

Pickering C, Kiely J (2017) Can the ability to adapt to exercise be considered a talent – and if so, can we test for it? *Sports Medicine Open* **3** 43.

Pletcher MJ, McCulloch CE (2017) The challenges of generating evidence to support precision medicine. *JAMA* **177** 561-2.

Plowman SA, Smith DL (2007) *Exercise Physiology for Health, Fitness and Performance.* Lipincott, Williams & Williams.

Poehlman ET, Tremblay A, Despres JP, Fontaine E, Perusse L, Theriault G, Bouchard C (1986) Genotype-controlled changes in body composition and fat morphology following overfeeding in twins. *American Journal of Clinical Nutrition* **43** 723-31.

Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH (2006) Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Circulation* **113** 898-918.

Potteiger JA, Jacobsen DJ, Donnelly JE, Hill JO (2003) Glucose and insulin responses following 16 months of exercise training in overweight adults: the Midwest Exercise Trial. *Metabolism* **52** 1175-81.

Prabhakaran B, Dowling EA, Branch JD, Swain DP, Leuthotz BC (1999) Effect of 14 weeks of resistance training on lipid profile and body fat percentage in premenopausal women. *British Journal of Sports Medicine* **33** 190-5.
Prasad V (2016) Perspective: the precision-oncology illusion. *Nature* **537** S63.
Precision Medicine Initiative Working Group. *Report to the advisory committee to the director: the precision medicine initiative cohort program-building a research foundation for 21st century medicine*. Washington DC. National Institutes of Health, 2015.
Prud'Homme D, Bouchard C, LeBlanc C, Landry F, Fontaine E (1984) Sensitivity of maximal aerobic power to training is genotype-dependent. *Medicine and Science in Sports and Exercise* **16** 89-93.
Ramirez J, van Duijvenboden S, Ntalla I, Mifsud B, Warren HR, Tzanis E, Orini M, Tinker A, Lambiase PD, Munroe PB (2018) Thirty loci identified for heart rate response to exercise and recovery implicate autonomic nervous system. *Nature* **9** 1947.
Rankinen T, Argyropoulos G, Rice T, Rao DC, Bouchard C (2010) CREB1 is a strong genetic predictor of the variation in exercise heart rate response to regular exercise: the HERITAGE family study. *Circulation. Cardiovascular Genetics* **3** 294-9.
Rasool M, Malik A, Naseer MI, Manan A, Ahmed Ansari S, Begum I, Qazi MH, Pushparaj PN, Abuzenadah AM, Al-Qahtani MH, Kamal MA, Pushparaj PN, Gan SH (2015) The role of epigenetics in personalized medicine: challenges and opportunities. *BMC Medical Genomics* **8** (S1) S5.
Raue U, Trappe Ta, Estrem ST, Qian HR, Helvering LM, Smith RC, Trappe S (2012) Transcriptome signature of resistance exercise adaptations: mixed muscle and fiber type specific profiles in young and old adults. *Journal of Applied Physiology (1985)* **112** 1625-36.
Reckelhoff J (2001) Gender differences in the regulation of blood pressure. *Hypertension* **37** 1199-1208.
Resende CM, Durso DF, Borges KB, Pereira RM, Rodrirues GKD, Silva JLP, Rodrigues EC, Franco GR, Alvarez-Leite JI (2018) The polymorphism rs17782313 near MC4R gene is related with anthropometric changes in women submitted to bariatric surgery over 60 months. *Clinical Nutrition* **37** 1286-92.

Robergs RA, Dwyer D, Astorino, T (2010) Recommendations for improved data processing from expired gas analysis indirect calorimetry. *Sports Medicine* **40** 95-111.

Rose EA, Partfitt G (2007) A quantitative and qualitative explanation of the individual differences in affective responses to prescribed and self-selected exercise intensities. *Journal of Sport and Exercise Psychology* **29** 281-309.

Rosenkilde M, Auerbach P, Reichkendler MH, Ploug T, Stallknecht BM, Sjodin A (2012) Body fat loss and compensatory mechanisms in response to different doses of aerobic exercise-a randomized controlled trial in overweight sedentary males. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology* **303** R571-9.

Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I (2000) Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: A randomized, controlled trial. *Annals of Internal Medicine* **133** 92-103.

Ross R, de Lannoy L, Stotz PJ (2015) Separate effects of intensity and amount of exercise on interindividual cardiorespiratory fitness response. *Mayo Clinic Proceedings* **90** 1506-14.

Rowell LB, Shepherd JT. *Handbook of Physiology: Exercise, regulation and integration of multiple systems.* 1996. New York.

Ryan R. Cochrane Consumers and Communication Review Group. Cochrane Consumers and Communication Review Group reviews: how to consider equity issues. http://cccrg.cochrane.org, February 2013 (accessed 15th April 2017).

Sabbahi A, Arena R, Kaminsky LA, Myers J, Phillips SA (2018) Peak blood pressure responses during maximum cardiopulmonary exercise testing novelty and significance. *Hypertension* **71** 229-36.

Safar ME (1989) Pulse pressure in essential hypertension: clinical and therapeutical implications. *Journal of Hypertension* **7** 769 –76.

Sainani KL (2018) The problem with "magnitude-based inference". *Medicine and Science in Sport and Exercise* **50** 2166-76.

Sala C, Santin E, Rescaldani M, Magrini F (2006) How long shall the patient rest before clinic blood pressure measurement? *American Journal of Hypertension* **7** 713-7.

Salonen JY, Salonen R (1993) Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* **87** S3 II56-65.
Sarzynski MA, Ghosh S, Bouchard C (2017) Genomic and transcriptomic predictors of response levels to endurance training. *Journal of Physiology* **595** 2931-9.
Savard R, Despres JP, Marcotte M, Bouchard C (1985) Endurance training and glucose conversion into triglycerides in human fat cells. *Journal of Applied Physiology (1985)* **58** 230-5.
Scharhag-Rosenberger F, Walitzek S, Kindermann W, Meyer T (2012) Differences in adaptations to 1 year of aerobic endurance training: individual patterns of nonresponse. *Scandinavian Journal of Medicine and Science in Sports* **22** 113-8.
Schmitz KH, Ahmed RL, Yee D (2002) Effects of a 9-month strength training intervention on insulin, insulin-like growth factor (IGF)-I, IGF-binding protein (IGFPB)-1, and IGFBP-3 in 30-50-year old women. *Cancer Epidemiology Biomarkers Prevention* **11** 1597-1604.
Schmitz KH, Jensen MD, Kugler KC, Jeffrey RW, Leon AS (2003) Strength training for obesity prevention in midlife women. *International Journal of Obesity* **27** 326-33.
Schubert MM, Sabapathy S, Leveritt M, Desbrow B (2014) Acute exercise and hormones related to appetite regulation: a meta-analysis. *Sports Medicine* **44** 387-403.
Schuit AJ, Schouten EG, Miles TP, Evans WJ, Saris WH, Kok FJ (1998) The effect of six months training on weight, body fatness and serum lipids in apparently healthy elderly Dutch men and women. *International Journal of Obesity* **22** 847-53.
Segal NL, Allison DB (2002) Twins and virtual twins: bases of relative body weight revisited. *International Journal of Obesity and Related Metabolic Disorders* **26** 437-41.
Senior AM, Gosby AK, Lu J, Simpson SJ, Raubenheimer D (2016) Meta-analysis of variance: an illustration comparing the effects of two dietary interventions on variability in weight. *Evolution Medicine and Public Health* **1** 244-55.
Senn S (1993) Suspended judgement of n-of-1 trials. *Controlled Clinical Trials* **14** 1-5.
Senn S (2001) Individual therapy: new dawn or false dawn? *Drug Information Journal* **35** 1479-94.
Senn S (2004) Individual response to treatment: is it a valid assumption? *BMJ* **329** 966-8.

Senn S (2016) Mastering variation: variance components and personalised medicine. **35** *Statistics in Medicine* 966–77.
Senn S, Rolfe K, Julious SA (2011) Investigating variability in patient response to treatment – a case study from a replicate cross-over study. *Statistical Methods in Medical Research* **20** 657-66.
Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Gaziano JM, Manson JE, Glynn RJ (2000) Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in men. *Hypertension* **36** 801-17.
Shaw K, Gennat HC, O'Rourke P, Del Mar C (2006) Exercise for overweight or obesity. *Cochrane Database of Systematic Reviews* **4** 112-7.
Sheikholeslami Vatani D, Ahmadi S, Ahmadi Dehrashid K, Gharibi F (2011) Changes in cardiovascular risk factors and inflammatory markers of young, healthy, men after six weeks of moderate or high intensity resistance training. *Journal of Sports Medicine and Physical Fitness* **51** 696-700.
Shephard RJ, Rankinen T, Bouchard C (2004) Test-retest errors and the apparent heterogeneity of training responses. *European Journal of Applied Physiology* **91** 199-203.
Shojaee-Moradie F, Baynes KCR, Pentecost C, Bell JD, Thomas EL, Jackson NC, Stolinski M, Whyte M, Lovell D, Bowes SB, Gibney J, Jones RH, Umpleby AM (2007) Exercise training reduces fatty acid availability and improves the insulin sensitivity of glucose metabolism. *Diabetologia* **50** 404-13.
Simoneau JA, Lortie G, Boulay MR, Marcotte M, Thibault MC, Bouchard C (1986) Inheritance of human skeletal muscle and anaerobic capacity adaptation to high-intensity intermittent training. *International Journal of Sports Medicine* **7** 167-71.
Sisson SB, Katzmaryk PT, Earnest CP, Bouchard C, Blair SN, Church TS (2009) Volume of exercise and fitness non-response in sedentary post-menopausal women. *Medicine and Science in Sports and Exercise* **41** 539-45.
Skinner JS, Jaskolski A, Jaskolska A, Krasnoff J, Gagnon J, Leon AS, Rao DC, Wilmore JH, Bouchard C (2001) Age, sex, race, initial fitness and response to training: the HERITAGE family study. *Journal of Applied Physiology (1985)* **90** 1770-6
Skinner JS, Wilmore KM, Jaskolska A, Jaskolski A, Daw EW, Rice T, Gagnon J, Leon AS, Wilmore JH, Rao DC, Bouchard C (1999) Reproducibility of maximal

exercise test data in the HERITAGE family study. *Medicine and Science in Sports and Exercise* **31** 1623-8.

Snyder KA, Donnelly JE, Jabobsen DJ, Hertner G, Jakicic JM (1997) The effects of long-term, moderate intensity, intermittent exercise on aerobic capacity, body composition, blood lipids, insulin and glucose in overweight females. *International Journal of Obesity* **21** 1180-9.

Songsorn P, Lambeth-Mansell A, Mair JL, Haggett M, Fitzpatrick BL, Ruffino J, Holliday A, Metcalfe RS, Vollaard NB (2016) Exercise training comprising of single 20-s cycle sprints does not provide a sufficient stimulus for improving maximal aerobic capacity in sedentary individuals. *European Journal of Applied Physiology* **116** 1511-7.

Sparks LM (2017) Exercise training response heterogeneity: physiological and molecular insights. *Diabetologia* **60** 2329-36.

Spear BB, Heath-Chiozzi M, Huff J (2001) Clinical applications of pharmacogenetics. *Trends in Molecular Medicine* **7** 201-4.

Stacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Milled ED, Simons-Morton DG, Karanja N, Lin PH (2001a) Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *New England Journal of Medicine* **344** 3-10.

Stacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, Simons-Morton DG, Karanja N, Lin PH (2001b) A clinical trial of the effects of reduced dietary sodium and the DASH dietary pattern (The DASH-Sodium Trial). *New England Journal of Medicine* **135** 1019-28.

Stefan N, Thamer C, Staiger H, Machicao F, Machann J, Schick F, Venter C, Niess A, Laakso M, Fritsche A, Haring HU (2007) Genetic variations in PPARD and PPARGC1A determine mitochondrial function and change in aerobic physical fitness and insulin sensitivity during lifestyle intervention. *Journal of Clinical Endocrinology Metabolism* **92** 1827-33.

Stubbs RJ, Hughes DA, Johnstone AM, Whybrow S, Horgan GW, King N, Blundell Jl (2004) Rate and extent of compensatory changes in energy intake and expenditure in response to altered exercise and diet composition in humans. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* **286** R350-R358.

Stubbs RJ, Sepp A, Hughes DA, Johnstone AM, King N, Horgan G, Blundell JE (2002a) The effect of graded levels of exercise on energy intake and balance in free-living women. *International Journal of Obesity* **26** 866-9.
Stubbs RJ, Sepp A, Hughes DA, Johnstone AM, Horgan GW, King N, Blundell J (2002b) The effect of graded levels of exercise on energy intake and balance in free-living men, consuming their normal diet. *European Journal of Clinical Nutrition* **56** 129-40.
Stunkard AJ, Foch TT, Hrubec Z (1986a. A twin study of human obesity. *JAMA* **256** 51-54.
Stunkard AJ, Sørensen TI, Hanis C, Teasdale TW, Chakraborty R, Schull WJ, Schulsinger F (1986b) An adoption study of human obesity. *New England Journal of Medicine* **314** 193-198.
Sui X, LaMonte MJ, Blair SN (2007) Cardiorespiratory fitness as a quantitative predictor of non-fatal cardiovascular events in asymptomatic men and women. *American Journal of Epidemiology* **165** 413-23.
Svetkey LP, Harsha DW, Vollmner WM, Stevens VJ, Obarzanek E, Elmer PJ, Lin PH, Champagne C, Simons-Mortin DG, Aickin M, Proschan MA, Appel LJ (2003) PREMIER: a clinical trial of comprehensive lifestyle modification for blood pressure control: rationale, design and baseline characteristics. *Annals of Epidemiology* **13** 462-71.
Svetkey LP, Erlinger TP, Vollmner WM, Feldstein A, Cooper LS, Appel LJ, Ard JD, Elmer PJ, Harsha DW, Stevens VJ (2005) Effect of lifestyle modifications on blood pressure by race, sex, hypertension status and age. *Journal of Human Hypertension* **19** 21-31.
Takahashi H, Yoshika M, Yokoi T (2015) Validation of three automatic devices for the self-measurement of blood pressure according to the European Society of Hypertension International Protocol revision 2010: The Omron HEM-7130, HEM-7320F and HEM 7500F. *Blood Pressure Monitoring* **20** 92-7.
Takeshima N, Rogers ME, Islam MM, Yarmauchi T, Watanabe E, Okada A (2004) Effect of concurrent aerobic and resistance circuit exercise training on fitness in older adults. *European Journal of Applied Physiology* **93** 173-82.
Tan LJ, Zhu H, He H, Wu KH, Li J, Chen XD, Zhang JG, Shen H, Tian Q, Krousel-Wood M, Papasian CJ, Bouchard C, Perusse L, Deng HW (2014) Replication of 6

obesity genes in a meta-analysis of genome-wide association studies with diverse ancestries. *PLos One* **30** e96149.
Tan S, Wang X, Wang J (2012) Effects of supervised exercise training at the intensity of maximal fat oxidation in overweight young women. *Journal of Exercise Science and Fitness* **10** 64-9.
Tan S, Wang J, Cao L, Guo Z, Wang Y (2016) Positive effect of exercise training at maximal fat oxidation intensity on body composition and lipid metabolism in overweight middle-aged women. *Clinical Physiology and Functional Imaging* **36** 225-30.
Tandy-Connor S, Guiltinan J, Kremely K, LaDuca H, Reineke P, Gutierrez S, Gray P, Tippin Davis B (2018) False-positive results released by direct-to-consumer genetic tests highlights the importance of clinical confirmation testing for appropriate patient care. *Genetics in Medicine* **doi:10/1038/gim.2018.38**
Tedstone AE (2016) Obesity treatment – are personalized approaches missing the point? *BMJ* **354** i4890.
Teixeira PJ, Going SB, Houtkooper LB, Metcalfe LL, Blew RM, Flint-Wagner HG, Cussler EC, Sardinha LB, Lohman TG (2003) Resistance training in postmenopausal women with and without hormone therapy. *Medicine and Science in Sports and Exercise* **35** 555-62.
The 100,000 Genome Project. https://www.genomicsengland.co.uk/the-100000-genomes-project/. Accessed 8th March 2018.
Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L (2001) The acute versus the chronic response to exercise. *Medicine and Science in Sports and Exercise* **33** (6 Suppl) S438-45.
Timmons JA, Knudsen S, Rankinen T, Koch LG, Sarzynski M, Jensen T, Keller P, Scheele C, Vollaard NB, Nielsen S, Akerstrom T, MacDougald OA, Jansson E, Greenhaff PL, Tarnopolsky MA, van Loon LJ, Pederson BK, Sundberg CJ, Wahlstedt C, Britton SL, Bouchard C (2010) Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *Journal of Applied Physiology (1985*) **108** 1487-96.
Topouchian J, Agnoletti D, Blacher J, Youssef A, Ibanez I, Khabouth J, Khawaja S, Beaino L, Asmar R (2011) Validation of four automatic devices for self-measurement of blood pressure according to the international protocol of the

European Society of Hypertension. *Vascular Health and Risk Management* ***7*** 709-17.

Tremblay A, Poehlman ET, Despres JP, Theriault G, Danforth E, Bouchard C (1997) Endurance training with constant energy intake in identical twins: changes over time in energy expenditure and related hormones. *Metabolism* **46** 499-503.

Toraman NF, Erman A, Agyar E (2004) Effects of multicomponent training on functional fitness in older adults. *Journal of Aging and Physical Activity* **12** 538-53.

Tracy BL, Hart CE (2013) Bikram yoga training and physical fitness in healthy young adults. *Journal of Strength and Conditioning Research* **27** 822-30.

Turnbull F, Neal B, Algert C, Chalmers J, Woodward M, MacMahon S (2003) Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* **362** 1527-35.

Unick J, Otto A, Goodpastor B, Helsel DL, Pellegrini CA, Jakicic JM (2010) Acute effect of walking on energy intake in overweight/obese women. *Appetite* **55** 413-9.

Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D (2002) Residual life-time risk for developing hypertension in middle-aged men and women: the Framingham Study. *JAMA* **297** 1003-10.

Vasan RS, Larson MG, Leip EP Evans JC, O'Donnell CJ, Kannel WB, Levy D (2001) Impact of high-normal blood pressure on the risk of cardiovascular disease. *New England Journal of Medicine* **345** 1291-97.

Vellers HL, Kleeberger SR, Lightfoot JT (2018) Inter-individual variation in adaptations to endurance and resistance exercise training: genetic approaches towards understanding a complex phenotype. *Mammalian Genome* **29** 48-62.

Vilela BL, Silva AABS, de Lira CAB, Andrade Mdos S (2015) Workplace exercise and educational program for improving fitness outcomes related to health in workers: a randomized controlled trial. *Journal of Occupational and Environmental Medicine* **57** 235-40.

Vollaard NBJ, Constantin-Teodosiu D, Fredriksson K, Rooyackers O, Jansson E, Greenhaff PL, Timmons JA, Sundberg CJ (2009) Systematic analysis of adaptations in aerobic capacity and submaximal energy metabolism provides a unique insight into determinants of human aerobic performance. *Journal of Applied Physiology (1985)* **106** 1479-86.

Warburton DE, Whitney Nichol C, Bredin SS (2006) Health benefits of physical activity: The evidence. *Canadian Medical Association Journal* **174** 801-9.

Washburn RA, Szabo AN, Lambourn K, Willis EA, Ptomey LT, Honas JJ, Herrmann SD, Donnelly JE (2014) Does the method of weight loss effect long-term changes in weight, body composition or chronic disease risk factors in overweight or obese adults? A systematic review. *Plos One* **9 e109849. doi: 10.1371/journal.pone.0109849**

Webborn N, Williams A, McNamee M, Bouchard C, Pitsiladis Y, Ahmetov I, Ashley E, Byrne N, Camporesi S, Collins M, Dijkstra P, Enyon N, Fuku N, Garton FC, Hoppe N, Holm S, Kaye J, Klissouras V, Lucia A, Maase K, Morna C, North KN, Pigozi F, Wang G (2015) Direct-to-consumer genetic testing for predicting sports performance and talent identification: consensus statement. *British Journal of Sports Medicine* **49** 1486-91.

Whalley AJ, Asher JE, Froguel P (2009) The genetic contribution to non-syndromic human obesity. *Nature Reviews Genetics* **10** 431-2.

Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J (2002) Primary prevention of hypertension. Clinical and public health advisory from the National High Blood Pressure Education Program. *JAMA* **288** 1882-88.

Whybrow S, Hughes DA, Ritz P, Johnstone AM, Horgan GW, King N, Blundell JE, Stubbs RJ (2008) The effect of incremental increase in exercise on appetite, eating behavior and energy balance in lean men and women feeding ad libitum. *British Journal of Nutritio*n **100** 1109-15.

Williams CJ, Williams MG, Eynon N, Ashton KJ, Little JP, Wisloff U, Coombes JS (2017) Genes to predict $\dot{V}O_2$max trainability: a systematic review. *BMC Genomics* **18** 831.

Williamson PJ, Atkinson G, Batterham AM (2017) Inter-individual responses of maximal oxygen uptake to exercise training: A critical review. *Sports Medicine* **47** 1501-13.

Williamson PJ, Atkinson G, Batterham AM (2018) Inter-individual differences in weight change following exercise interventions: A systematic review and meta-analysis of randomised controlled trials. *Obesity Reviews* **19** 960-5.

Wilmore JF, Despres JP, Stanforth PR (1999) Alterations in body weight and composition consequent to 20 wk of endurance training: the HERITAGE Family Study. *American Journal of Clinical Nutrition* **70** 245-52.

Wilmore JH, Stanforth PR, Gagnon J, Rice T, Mandel S, Leon AS, Rao DC, Skinner JS, Bouchard C (2001) Heart rate and blood pressure changes with endurance training: the HERITAGE family study. *Medicine and Science in Sports and Exercise* **33** 107-16.

Wishnofsky M (1958) Caloric equivalents of gained or lost weight. American Journal of Clinical Nutrition **6** 542-6.

Wolz M, Cutler J, Roccella EJ, Rohde F, Thom T, Burt V (2000) Statement from the National High Blood Pressure Education Program: Prevalence of hypertension. *American Journal of Hypertension* **13** 103-4.

World Health Organization (2016) Global report on diabetes. http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf;jsessionid=13204DC8140DC842CC8A6E6A58FA9099?sequence=1&TSPD_101_R0=e613876c4e5cea83ea28ddcbeeb9713fh2T000000000000000027839ed96ffff0000000000000000000000000005ba396af0058493fbb

Yildiran T, Koc M, Bozkurt A, Sahin DY, Unal I, Acarturk E (2010) Low pulse pressure as a predictor of death in patients with mild to advanced heart failure. *Texas Heart Institute Journal* **37** 284-90.

Yzaguirre I, Grazoli G, Domenech M, Vinuesa A, Pi R, Gutierrez J, Coca A, Brugada J, Sitges M (2017) Exaggerated blood pressure response to exercise and late-onset hypertension in young adults. *Blood Press Monitoring* **22** 339-44.

Zadro JR, Shirley D, Andrabe TB, Scurrah KJ Bauman A, Ferreira PH (2017) The beneficial effects of physical activity: Is it down to your genes? A systematic review and meta-analysis of twin and family studies. *Sports Medicine-Open* **3**:4.

Zucker DR, Ruthazer R, Schmid CH (2010) Individual (n-of-1) trials can be combined to give population comparative treatment effect estimates: methodologic considerations. *Journal of Clinical Epidemiology*. **63** 1312-23.e.